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Section of Pædiatrics

President—J. VERNON BRAITHWAITE, M.D., F.R.C.P.

[*May* 25, 1956]

DISCUSSION ON TUBERCULOUS CERVICAL ADENITIS

Dr. F. J. W. Miller (Royal Victoria Infirmary, Newcastle upon Tyne):

The Problems of Peripheral Tuberculous Lymphadenitis in Childhood

I shall discuss only our own experience of this form of tuberculosis.

I shall consider not only cervical adenitis but also superficial or peripheral tuberculous adenitis in any part of the body, for it is all part of the same problem. My own interest arose as part of a wider concern with childhood tuberculosis and, in particular, from a study of the behaviour of glands in a group of children with visible primary infection on skin or mucosa (Miller and Cashman, 1955). This, in turn, broadened into a wider study of all the cases seen in our department in Newcastle over a period of seven years, made in an attempt to answer four major questions.

(1) What is the origin of peripheral tuberculous lymphadenitis?
(2) What is the natural history if untreated?
(3) What is the variation of the clinical picture?
(4) What is the most effective method of treatment?

Three basic conditions must be fulfilled before the natural history of tuberculosis can be studied.

(i) The time, within defined limits, and site of primary infection must be known.
(ii) A large group of children of all ages must be studied (ideally all the children in a population).
(iii) The study must continue long enough to see the ultimate manifestations of clinical disease.

Very few studies of tuberculous lymphadenitis satisfy these conditions, and this is perhaps the major reason why our knowledge is so uncertain.

How do peripheral tuberculous glands arise.—We think that wherever this occurs in childhood, it is almost always the glandular component of a primary complex, either the primary glands themselves (the first affected glands) or glands farther down the same lymphatic chain. There are exceptions to this, but they are uncommon. Some of our evidence is given in Fig. 1, showing the distribution of adenitis in 168 children with peripheral lymphadenitis.

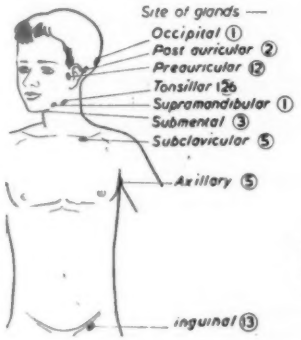

FIG. 1.—Distribution of peripheral tuberculous lymphadenitis in 168 children (Boyes *et al.*, 1956).

In 125 it was the *only* evidence of the primary infection and in another 33 there was, in addition, other evidence of primary calcification indicated by calcification of the root of the lung (17) or in the abdomen (16), including 2 with calcification in both chest and abdomen. In all cases other than those in the tonsillar or submandibular glands, we knew the precise site of the primary focus. But one of the real difficulties in detecting the primary focus in the oro-pharynx is that it is visible for only a limited time and may disappear without leaving

a scar. This phenomenon is clearly seen in Figs. 2 and 3, showing a permanent tooth erupting at the site of a primary focus in the crater of the preceding deciduous tooth. Thus, on clinical grounds, we feel that peripheral lymphadenitis is an expression of primary infection and therefore suggest that primary infection, outside the chest and abdomen, is much more common than we have formerly believed.

FIG. 2.—Circular ulcer at site of tooth extraction.

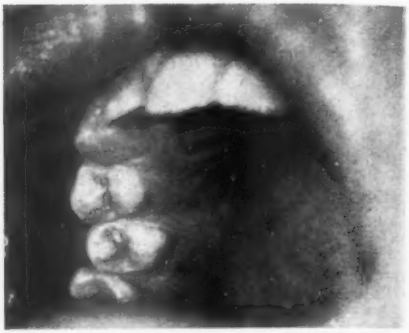

FIG. 3.—Same case as Fig. 2. Eighteen months after infection the site of primary infection has been obliterated by the permanent tooth (Boyes *et al.*, 1956).

Figs. 2 and 3 are from *Arch. Dis. Childh.* (1956) by kind permission.

What is the natural history of peripheral lymphadenitis?—We have found that the great majority of untreated peripheral tuberculous glands sooner or later soften and form abscesses which rupture spontaneously. Indeed, only 15 from 230 cases followed over a minimal period of two years did not give rise to abscess formation; sometimes softening did not occur for four to five years after infection. This tendency to soften should be the central fact in determining treatment; once softening and spontaneous rupture have occurred the period of illness is likely to be long.

If spontaneous softening has once occurred in a gland we found that in almost half the cases there was a further gland abscess either at the site of the primary gland or further down the same lymphatic chain.

Glands tend to soften after intercurrent infection, especially upper respiratory infections. This is not due to direct invasion of the gland by other organisms, for the pus obtained from the abscess is either sterile or contains only tubercle bacilli, but is due to a temporary diminution of the patient's resistance, possibly together with increased gland activity. For example, a child presented with simultaneous softening of the pre-auricular, tonsillar and post-sterno-mastoid glands three years after primary infection of skin of the forehead and immediately after measles.

The incidence of hæmatogenous complications in children with peripheral lymphadenitis is of the same order as in primary infection of chest or abdomen, but children with primary infection in the lungs or abdomen only very rarely get peripheral lymphadenitis as a result of hæmatogenous spread.

Clinical picture of peripheral lymphadenitis.—Two major groups of cases are seen:

(i) Children with lymphadenitis after recent infection.

(ii) Children with softening in glands infected more than one to two years previously.

Children with glands appearing at the time of primary infection present the same spectrum of reaction to primary infection as children with infection in the lungs or abdomen. There are only two differences; when the infection is in the lungs the glands are not visible, but on the other hand, the child with peripheral lymphadenitis escapes the danger of bronchial involvement. In the majority of children there is some diminution of zest and vigour with a slow progressive enlargement of the regional gland, which is clinically the largest gland, and its satellites, to form a group of smaller glands about the regional; sometimes these glands proceed slowly but inevitably to softening, in others they subside only to enlarge again some time thereafter.

In about one-tenth of the cases the reaction is much more acute; the child is sharply febrile with a temperature ranging from 101° to 104° F., he is highly sensitive to tuberculoprotein and may develop erythema nodosum. The glands enlarge much more rapidly and

become one mass: they may appear hot and rather tender but are never so tender as in acute pyococcal adenitis and do not restrict function. These glands soften very rapidly and even with chemotherapy abscess formation occurs within a month or so.

Softening in old glands.—If softening occurs in glands infected a year or more earlier, calcification is often visible on radiological examination. The child is not so well as usual, but acute symptoms or more severe disturbances, and the acute reaction described above, do not occur. The softening is usually rapid and the skin may be involved in two to three weeks once the abscess has become apparent.

What is the most effective treatment of tuberculous lymphadenitis?—The objects of treatment can be described as follows:

(*a*) To avoid abscess formation and skin involvement.
(*b*) To avoid a long period of ill-health or hospital treatment.
(*c*) To obtain a good cosmetic result.

If the glands are seen shortly after infection and before they soften, it is usually possible to attempt all three objectives, but often softening is present before the child is seen and then only the second and third of these criteria can be pursued.

I have no experience with calciferol or with X-ray therapy and shall not consider these methods here.

Effect of chemotherapy on glands.—Can glands which are firm when first seen be prevented from softening by chemotherapy alone? We found that with an initial course of streptomycin and PAS for three to four weeks the glands first become smaller and more discrete, but once the chemotherapy has been stopped the glands sooner or later have softened. Since the introduction of isoniazid and the use of longer courses of therapy, we still do not know if isoniazid and PAS, given over long periods, will prevent softening until firm calcification has occurred. I have a small group of children on such treatment, but it will be at least two to three years before I get the answer.

With our present knowledge of the natural history of tuberculous lymphadenitis and of the action of antibiotics, we must rely upon a combination of surgery and antibiotics.

The best results are achieved when the glands are firm and recent when first seen and the child has not had a marked febrile reaction. If streptomycin and isoniazid are given there is both a general and local effect. The general condition improves rapidly and at the same time the gland mass shrinks and sometimes resolves into separate discrete glands. This reduction in size will continue for about three weeks, but the glands do not return to normal and usually one remains larger than the others. I believe, subject only to the possible effect of long-term isoniazid and PAS, that the correct advice at this stage is to remove by *local* dissection 2 or 3 of the largest glands, but not with a block dissection. A planned incision gives a good cosmetic result and none of the 20 cases we have done at this stage have had subsequent abscesses. The antibiotics should be continued over the period of operation and then isoniazid and PAS given for three months afterwards.

Recent infection with a marked febrile reaction.—This reaction is uncommon but dramatic. The effect of streptomycin and isoniazid is also striking, the temperature falls and the gland then gets smaller rapidly (Fig. 4). But softening also occurs rapidly in two to three weeks,

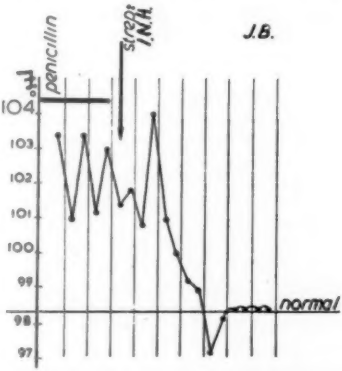

FIG. 4.—Fall in temperature after commencing streptomycin and isoniazid.

and immediate operation at this stage is advisable as the best method of reducing the time of illness. Isoniazid and PAS should be continued for a further three months.

If the glands are soft when first seen antibiotics are certainly not sufficient to prevent further softening and skin involvement, and the pus and caseous material must be removed. Aspiration has been very disappointing even with constant isoniazid and PAS administration, and the shortest period of morbidity occurs when the pus is drained through a small incision and any caseous material present also removed: the wound can either be closed or a small drain left in for two to three days. But, whenever tuberculous glands are seen in this later stage of softening after delayed breakdown, there is always the chance of further abscess formation at the same site or in adjacent glands, and prolonged chemotherapy should be given.

This account of the treatment of tuberculous glands is necessarily incomplete, partly because the disease has such a prolonged natural history, partly because we are still gaining experience with the newer antibiotics, especially isoniazid; it is also because the treatment presents such a wide variety of clinical problems and varying conditions in the glands that my descriptive grouping is in great danger of oversimplification. Yet, even in the acute cases with soft glands and red skin, the cosmetic results are usually much better than first appearance would indicate. Patience, personal care and prolonged antibiotics are probably more important than the precise method of operative technique.

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Mr. Denis Browne:

Physiology.—In discussing most systems of the body, such as the nervous, the vascular, or the muscular, it can be taken for granted that their function is understood and that there is a large amount of reasonably accurate information about it. The function of the lymphatic system, apart from the absorption of fats by a limited and specialized portion of it, remains a mystery. The explanations of its workings given in textbooks are either rationalizations of theological outlook . . . "that it wouldn't be there if it hadn't some good purpose" or else due to an almost equally unscientific application of the Darwinian formula of the survival of the fitter. According to this rather inadequate hypothesis only structures which add to the chances of survival, or in other words, have a useful function, are present in the body. This overlooks the fact that some parts, such as the male breast and the toenails, certainly have no function. (It is occasionally necessary to point out that an unproved suggestion that structures may have had a function in different ancestral types is not to give them a function in the present.)

One of the principles of science, in which it differs from politics and theology, is the admission of ignorance. Following this principle we must begin any discussion of such a part of the lymphatic system as the glands of the neck by saying that we are quite ignorant of any purpose they serve, and that we must consider the possibilities that they have no function at all, and are consequently simply a liability, a weak spot in the defences of the body. Supposing, for instance, that all the lymphatic glands of the neck had been removed by dissection, would the resistance of the body to tubercle be any less? If not, what is the meaning in the economy of the body of the infection we are discussing?

Anatomy.—Groups of lymph glands drain particular areas, and in these areas there are particular structures which are apt to cause the majority of their infections. In the chest, for instance, the lungs are the main origin of adenitis, and in the abdomen the bowel. Such sources as tubercular skin ulcers or arthritis may occur in the neck as almost anywhere else; but the most common origin of cervical adenitis is the accumulation of lymphatic tissue in the tonsils and adenoids. These strange structures, so vaguely and inaccurately described in books of anatomy and so often inefficiently attacked by surgeons, have never been proved to have any function at all. At the present time it is usually taught that their purpose is to increase the body's resistance to infections which lodge in the ideal bed for multiplication which they provide. Clinically there is no ground whatever to support this hypothesis; chronic infections of the throat cease when they are cleanly removed, and no diminution of general resistance to infection can then be demonstrated.

Though many papers have been published on the subject, it is strange how little tubercular infection of the lymphatic structures of the nasopharynx is realized by the profession at large. I have been present at a discussion of the indications for tonsillectomy at this Society in which tubercle was not mentioned at all by the leading speakers. Another aspect of ignoring this infection is the advice in most textbooks of surgery to obtain an oto-rhino-laryngologist's opinion on whether the tonsils are "infected" in cases of tubercular adenitis; and only then to remove them. As something like 70% of tonsils in such cases show gross tubercle, and as the tubercular tonsil is often small, pale and innocent looking, I do not consider this sound advice.

From this source two distinct forms of infection habitually invade the cervical lymph glands, either separately or in combination. One is tubercle, and the other may be called coccal, since it is usually streptococcal though occasionally staphylococcal. Presumably both infections are either inhaled or swallowed, and gain a first lodging, as diphtheria usually does, in the ideal breeding ground provided by the moist, warm, sheltered crypts of the tonsil.

Consideration of these processes prompts some interesting lines of thought as to the possible connexion between tubercle of the tonsils and tubercle of the lungs. Tuberculous infection of the larynx usually occurs from bacilli passing upwards in sputum, but may also occur from their passage downwards in mucus from the nasopharynx. It is well recognized clinically that coccal infections of the tonsils and adenoids may pass downwards and cause infections of the lungs such as bronchitis. Is it impossible that a similar process may exist with tubercle? I once carried out fifty successive removals of tonsils and adenoids in unselected cases of thoracic tubercle in children. In over 30% of these cases the removed tissue showed gross tuberculous infection, and most striking clinical improvements in the chest condition occurred in many cases; none were harmed. I think more work along these lines is justified. It is occasionally asserted that lymph glands may be infected with tubercle bacilli carried by the blood stream. I know of no proof of this, and as in all cases there is an obvious line of infection along lymphatics I think that this must be very rare if it occurs at all.

The coccal infection typically has an acute or subacute course, in contrast to the slow chronic increase or decline in tuberculous infections. The combination of the two infections often produces a characteristic pattern of illness, with comparatively rapid increases and decreases of coccal origin masking a slow and steady progress of tubercle. The tuberculous infection goes through the well-known stages of simple bacterial invasion, giant cell formation and caseation; but then may take either of two courses. The infection may die out and the gland necrose aseptically, so that finally only unabsorbable calcium salts formed in the caseations remain; or it may form pus which inevitably, if left to itself, discharges through the skin. The tendency to the formation of pus, so much more common in the neck than in the chest or abdomen, seems to have a connexion with secondary coccal infections. Frequently a simple tuberculous adenitis, after remaining hard and unchanged for years, suddenly develops an abscess following a coccal tonsillitis.

Once the discharge of tuberculous pus has started it continues till the necrotic gland tissue at the bottom of the sinus has slowly dissolved; a process that may take years unless shortened by some form of surgery. While the tubercle bacilli in the pus are passing the skin they produce a typical effect upon it, a thinning and final necrosis starting from the deeper layers. The process differs in an interesting way from either tuberculous infection of a skin wound, or from lupus. It resembles tuberculous laryngitis, in that it depends upon the constant contact of tubercle bacilli and ceases as soon as this contact does.

Diagnosis.—The early stages of Hodgkin's disease may resemble tuberculous adenitis, and in any cases of doubt a biopsy should be made. It is occasionally difficult to make out whether a subacute coccal infection has an underlying tuberculous element, but on the system of treatment recommended the point is of no clinical importance. An X-ray will often settle the question by showing calcification in the glands.

Treatment.—From this description the aims of surgery are obvious. The first is the elimination of the source of the infection, as this can be done without damage to the body as a whole. I was taught many years ago by the late George Waugh that the first step in treating tuberculous cervical adenitis was to remove the tonsils and adenoids without delay, and I still regard this as sound advice.

The second aim is to cut short the long period of discharge from sinuses which is the unassisted reaction of the body. On this aim there are wide differences of opinion and no method guarantees easy and rapid success. The main ones are:

Excision: When I first began the study of these cases the popular teaching was that the entire mass of glands should be cut out, preferably before abscesses occurred. This was a severe and difficult operation which at the best left a large scar and a disfiguring flattening of the side of the neck owing to the removal of the subcutaneous tissues. It was also only possible to remove the obviously infected glands, and only too often others showed up later; the argument so often made that excision settled the problem once and for all was far from accurate. In consequence more conservative measures were tried.

Aspiration: Aspiration of abscesses was quite ineffective, as it did not remove the necrotic gland and the lumps of caseous material that invariably were present.

X-rays: X-rays were sometimes applied, but apart from the well-known dangers of this treatment it had no obvious effect. It must be remembered that subacute coccal infection, already mentioned as being often difficult to distinguish from tuberculosis, subsides spontaneously, and this may often have confused the issue.

Streptomycin: Streptomycin seems to have little influence upon an established tuberculous adenitis and for such a comparatively benign condition a full course of this drug is a severe infliction upon a child, apart from its dangers.

Curettage of abscesses, either when they have spontaneously discharged or after incision is often satisfactory, but there is the difficulty of knowing the exact location of the necrotic tissue which it is desired to remove.

Incision and expression are my own practice, and I think they are the most satisfactory of all. The tonsils and adenoids are removed as soon as possible; if an abscess has already formed there is no objection to combining this operation with its expression. If there is no abscess, nothing is done unless one forms. If this occurs the process is watched till the skin is just adherent over the softening spot, and then an incision a centimetre long is made through which the pus escapes and the necrotic gland is squeezed out of the opening by strong pressure applied by the fingers, with a piece of gauze under them to give a grip and hold the expressed matter. This squeezing is repeated, usually at least a dozen times, till three successive applications of the full force of one's fingers produce nothing but blood. This means that all the necrotic tissue has been expressed, and all that is then necessary is to keep the small opening patent till healing of the large cavity under it is complete. The objection made to this method that it will "spread the infection" is in my experience of several hundred cases quite baseless. The difficulty in getting it applied is that few will use sufficient force and persistence in applying pressure.

If a sinus has persisted for some time there is always contraction of scar tissue along its course, which gives the characteristic indrawn appearance of the skin where it opened. Excision of the scar several years after the infection has subsided, combined with a careful suturing of the subcutaneous fatty tissues, will often make a very marked improvement.

[*June* 16, 1956]

MEETING IN THE ANATOMY SCHOOL, DOWNING STREET, CAMBRIDGE

The Decline and Fall in Hospital Pædiatrics

By DOUGLAS GAIRDNER, D.M., F.R.C.P.

In many places in this country, notably in London, the diminishing needs for hospital beds for children have led to a situation where more beds are available than are needed. In the area around Cambridge there has, for various reasons, been an actual shrinkage in the numbers of hospital beds available for children, so that, although the number of sick children requiring hospital care has declined here as elsewhere, there is still some shortage of hospital beds.

This area, with a population of 287,000, comprises Cambridge and those parts of the adjacent counties of Cambs, Hunts, Essex, Herts and Isle of Ely which are either served by the Cambridge group of hospitals, or by hospitals closely linked to them. The area is self-sufficient for all hospital services with the exception of neurosurgery and cardiac surgery, but to balance this receives from outside some pædiatric cases requiring specialist services.

Table I shows the number of hospital beds for children available in the area, and for

TABLE I.—NUMBER OF HOSPITAL BEDS FOR CHILDREN

	Cambridge and surrounding area Pop. 287,000	Newcastle Pop. 295,000
E.N.T. cases	26	12
Long-stay cases (tubercle, orthopædic)	10	40
All other pædiatric cases, including infectious, but excluding prematures ..	48	110
Total	84	162
Total per 100,000	29	55

comparison, the figures published by Spence and Taylor (1954) for Newcastle for the year 1950. The two areas have about the same population, but differ widely in standards of living—housing, for instance, being relatively good in the Cambridge area, and poor in Newcastle.

From these figures it will be seen, (1) that the total number of children's beds in use in this area is little more than half that considered necessary in Newcastle in 1950. A more recent estimate by Dr. Mary Taylor (personal communication) is that in 1955 about 20% fewer beds were needed in Newcastle than in 1950, but the difference between the two areas still remains striking, particularly in respect of the number of long-stay cases. (2) In this area E.N.T. beds for children number nearly one-half of those for all other types of case, the main cause of admission being for tonsillectomy.

The main factors responsible for the declining need for children's beds are well known. They include the rising standard of infant care and feeding; the lowered incidence of certain infective diseases such as gastro-enteritis and tuberculosis; and the existence of potent anti-bacterial drugs and their ready availability to all, enabling much infective illness to be treated early by the family doctor. In an area like that of Cambridge where the average standard of housing is relatively good, and where the quality of medical care provided by the family doctor is also high, these factors all operate conspicuously. In addition, where home conditions are adequate the pædiatrician and family doctor, working in close co-operation and making use of the domiciliary consultation scheme and of the services of the district nurse or midwife, can often investigate and treat serious illness partly or wholly in the home. This trend is helped also by the increasing number of patients who have access to a car, and who can thus maintain frequent contact with the hospital. Some examples may be quoted.

Pyloric stenosis.—Early diagnosis enables operation to be carried out soon after admission, normal feeds are resumed about twenty-four hours after operation and the baby returns home a day or two later. Thus of 85 cases treated in one children's department over the past seven years, mostly by surgery, three-quarters stayed in hospital seven days or less, and nearly half for four days or less, with no deaths.

Herniotomy.—Many surgeons now allow children to return home the day after operation, returning later for removal of sutures.

Tuberculosis.—The advent of chemotherapy has made it possible both to shorten materially the duration of treatment, and to conduct much of this treatment at home, where injections of streptomycin can be given by the district nurse.

Metabolic investigations.—With ingenuity and a keen mother many of these may be carried out with the child remaining at home, for instance fat excretion tests, and rough but informative calcium balances.

Conclusions.—At the present time, home doctoring and hospital doctoring may interlock so closely that sharp boundaries between the two cease to exist, enabling much childhood illness to be investigated and treated without recourse to hospital admission, or with only a brief stay in hospital. The pædiatrician should be easy of access, and available to advise the family doctor by telephone or by consultation in the home twenty-four hours a day and seven days a week. For this reason a pædiatric centre should be based on at least two pædiatricians, and this also has the advantage of providing a choice both to the family doctor and to the patient. The size of population which these two pædiatricians can properly serve seems to be of the order of 300,000 to 350,000. Where standards of living are reasonably high, the number of hospital beds for children, *excluding* only those for E.N.T. cases and for prematures, may require to be no more than 25–30 per 100,000 population.

REFERENCE

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The Use of Hospital and Domiciliary Resources in the Modern State

By REGINALD LIGHTWOOD, M.D., F.R.C.P.

IN the early years of the present century the scale of hospital provision was made subject to available funds according to the needs then existing for the diagnosis and treatment of poor people who were seriously ill. The levels of prosperity and health now being achieved were then quite unexpected and would have seemed virtually impossible to the former leaders of the hospital world.

The effect on hospital work is likely to be seen first of all in children's departments and hospitals, because the fall in child morbidity is greater than the fall in adult morbidity and the birth-rate has diminished.

In economically prosperous Western states these factors have already eased the pressure on children's beds and facilitated the admission of children with minor illness. Empty beds

which were formerly rare in this country, are now common, and analyses of ward admissions will often show a high proportion of children not really in need of hospital treatment. Thus we made such an analysis at St. Mary's Hospital before the institution of a home care project and found that about one-quarter of the children in hospital, during a review period, had been admitted for conditions which could have been managed at home if the general practitioners had possessed the facilities and ability required, and there were also children whose stay in hospital could have been shortened.

Pædiatric bed requirements must vary according to local conditions and it seems probable that certain Scandinavian cities have over-provided children's beds so that some hospitals have, for a period of years, found it difficult to keep pædiatric beds in full activity and the proportion of relatively minor cases may then rise to well over 50%.

Doctors and nurses devoting themselves to hospital work do not like to see many vacant beds. Moreover, in the case of our training schools for sick children's nurses, the requirements of the General Nursing Council demand that a certain level of occupied beds be maintained. Again, in the case of a teaching hospital, it is felt that sufficient "clinical material" must be provided for clerking and teaching: but even this apparent need to keep a sufficient number of beds occupied for the instruction of undergraduate students should not be allowed to influence the filling of beds.

Pædiatricians were among the first to recognize the disadvantages to the patient of hospital care, believing that each admission should be justified by compelling medical or social indications. They also hold that child in-patients should not be treated in adult wards.

The present revolution in medical practice is showing its effects in different ways and at different times from place to place. It is our major pædiatric problem. Each pædiatric physician should make himself fully aware of the local factors in his area and be ready to advise his hospital authorities of the ways in which their clinical objectives should be modified to meet the changing situation. Along with consideration of bed requirements and out-patient staffing there should be consultation with general practitioners, health authorities and members of the lay public.

The analysis made by Dr. D. Gairdner gives a picture of pædiatrics in a city with a high standard of living and a high standard of family doctoring, surrounded by a fairly prosperous rural community with a close liaison between the pædiatricians and the family doctors. The pattern in some of our cities is different. St. Mary's Hospital, Paddington, is surrounded by a densely populated and relatively poor area serviced by practitioners who work under conditions less favourable than in Cambridge. The hospital provision is fully adequate for pædiatrics and for most of the year there is no shortage of beds. The Local Medical Committee of the County of London, the County Health Authority and the Board of Governors of the hospital have all shown themselves willing to support a pædiatric home care scheme with the following objectives:

The primary aim is to enable the hospital pædiatric staff to co-operate more closely with family doctors by giving them professional support and a ready service of modern diagnostic and therapeutic methods.

The second aim is the prevention of unnecessary use of hospital beds.

A third and subsidiary aim is to cut the high cost of in-patient treatment by providing an alternative which affords, nevertheless, a standard of care as high as the hospital ward can provide.

These objectives have been tackled by providing a home care pædiatric team, based at St. Mary's Hospital, which is available to give support to family doctors in caring for children who would otherwise have been transferred to hospital. In addition to saving admissions and preventing unhappiness it has helped to establish excellent working relationships with many doctors. For the hospital there is a sparing of beds, which can be used for more suitable cases, and the character of the cases coming into the ward has changed. We have also found that hospital trained staff have gained valuable insight and experience from working closely with the doctors in the homes of patients.

Surgical Problems in the Treatment of Birthmarks

By L. M. Rouillard, F.R.C.S.(Ed.)

Of the common birthmarks, the vast majority fall into four main groups:

(1) Strawberry marks or mixed hæmangiomata, often with a deep element beneath the skin lesion.
(2) Pigmented moles.
(3) Capillary hæmangiomata or port-wine stains.
(4) Cavernous hæmangiomata, with the deep element predominating and the skin lesion often minimal.

Each group presents its own special problem in treatment, and an attempt is made at the first interview to decide on a suitable plan. This plan is of particular importance for anxious parents, especially when a decision is taken against active treatment. A reasonably accurate prognosis can usually be made at the outset.

Where surgical intervention is necessary, the time factor should be taken into account, and there are three main age periods:

(*a*) *Two years:* As infants stand blood-loss badly, major surgical procedures should, if possible, be deferred until after this age.

(*b*) *School age:* Birthmarks which may be a source of embarrassment and emotional disturbance, should generally be removed before this time.

(*c*) *Puberty:* Malignant change is practically unknown in birthmarks before puberty, even under the influence of trauma. Surgical liberties may be taken which could not be countenanced after puberty.

The problem of birthmarks being essentially a cosmetic one, the following general lines of treatment are considered:

(1) *Strawberry marks or mixed hæmangiomata.*—This type presents initially as a uniformly red surface lesion, with a deep element whose development may be delayed. Most commonly the deep element is compact, and the lesion classically is first noticed two to three weeks after birth, grows steadily for six to nine months, and then begins to fade and shrink. Grey patches first appear, which spread and coalesce. Treatment is contra-indicated, or confined to removal of any fibrous remains about school age, if resolution is not complete by then. Less commonly the deep element is cavernous, and here the lesion is often present at birth, is prone to more rapid spread, and shows less tendency to spontaneous resolution. Sclerosing agents may be used to control the initial growth and to encourage fibrosis. Injections of concentrated saline (Matthews, 1953), repeated if necessary, have proved safe and effective Excision should be postponed until after the age of 2 years.

(2) *Pigmented moles.*—Here the problem is entirely surgical, the lesions being almost invariably present at birth, and showing little tendency to change. Simple excision at any age suffices for small moles, but lesions of moderate size may be removed in stages by the method of serial excision. Sections are removed at intervals of six to twelve months, and the natural elasticity of the skin permits even quite large moles to be excised in this way, leaving only a linear scar.

When replacement by a skin graft is necessary, because of the size or situation of the lesion, a full-thickness (Wolfe) graft is preferred as giving the best chance of good colour and texture and showing little tendency to contract. Post-auricular skin can be relied on to give an excellent colour match on the face and eyelids. For extensive moles, the risks of poor colour match and texture inherent in thin split-skin grafts must be accepted. Hynes (1956) has described a method of removing large pigmented moles with a razor down to the deep layers of the dermis, and covering with a split-skin graft of similar thickness, thus avoiding tedious scalpel dissection and minimizing joining scars.

(3) *Capillary hæmangiomata or port-wine stains.*—The treatment of these often presents the greatest difficulty. There is little tendency to spontaneous improvement, and often the skin is of normal texture, with only faint staining. Surgery is normally limited to the deeply coloured varieties, as a graft may be of poor texture and colour which is more disfiguring than the original lesion. Thermal agents or beta-radiation may be used to promote fading. Repeated painting with Thorium-X is safe and simple, but results are variable.

(4) *Cavernous hæmangiomata.*—The depth and variety of these lesions, and their extensive vascular communications, make primary surgery difficult and often dangerous. Repeated hæmorrhage, or rapid extension to involve vital structures, may demand early intervention. In general, however, every effort should be made to avoid operation in infancy. If injections of sclerosing fluids or the use of interstitial diathermy coagulation fail to arrest spread, treatment by radium or deep X-rays may be justifiable. The danger of producing late radiation changes is accepted in that final surgical repair may be more safely undertaken as a planned procedure rather than as an emergency. Great care must be taken near underlying cartilage, developing epiphyses, or breast tissue. Very good results have been reported by Brown and Fryer (1952), using radon seeds, either alone or combined with later surgery, of only 1/10 mc. per c.c.

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Milk Ejection and Mammary Engorgement

By B. A. Cross, M.A., Ph.D., M.R.C.V.S., and I. A. Silver, M.A., M.R.C.V.S.

The importance of the milk-ejection reflex in breast feeding is now well recognized (Gunther, 1955; Isbister, 1954). The reflex mechanism appears to be similar in all species so far studied (rat, rabbit, cat, dog, sheep, goat, cow and woman) and is illustrated diagrammatically in Fig. 1A. The stimulus of suckling excites, by undefined neural pathways, the

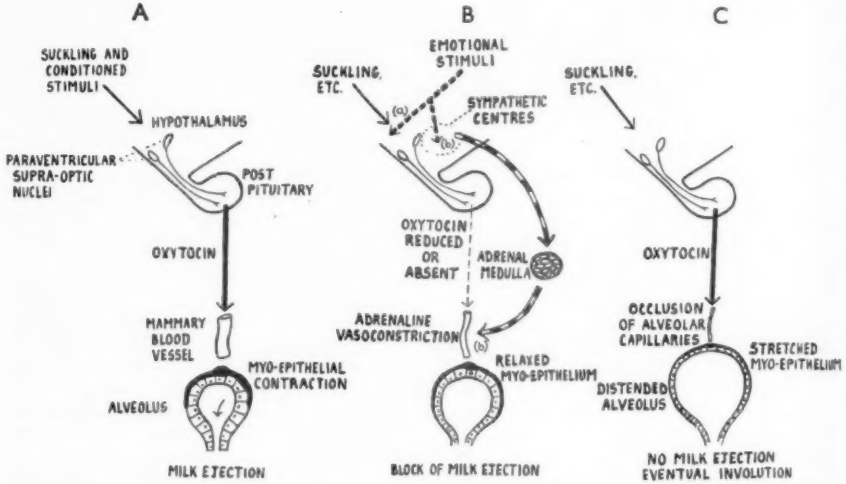

Fig. 1.—A, Normal milk ejection. B, Emotional inhibition of milk ejection: (*a*) Central inhibition of oxytocin release; (*b*) Peripheral sympathetico-adrenal inhibition. C, Mammary engorgement (non-removal of milk).

hypothalamic nuclei (paraventricular and supra-optic) innervating the posterior pituitary gland and this causes a release of oxytocin which circulates in the blood stream to the mammary gland where it stimulates contraction of the myoepithelial cells with resulting ejection of milk. (For reviews of experimental evidence *see* Cross, 1955*a*, 1956.)

The neuro-hormonal reflex just outlined is subject to a variety of central and peripheral modifying influences. Thus narcotic drugs, including for example alcohol and barbiturates, by depressing central excitability may block the reflex release of oxytocin. The reflex is readily conditioned to stimuli other than suckling and this fact implies a degree of cortical control. Among peripheral influences three may be mentioned. The viscosity of the milk largely determines the speed of passage of the milk along the fine lactiferous ducts, and hence the thickening of the milk that follows a prolonged non-suckling interval impairs the efficiency of milk ejection. The calibre of the minute blood vessels of the mammary gland controls the accessibility of circulating oxytocin to the contractile tissue; constriction of these vessels therefore reduces the degree of myoepithelial contraction (Cross, 1955*b*). Finally the normal reactivity of the myoepithelial cells is reduced by hypocalcæmia (Peeters *et al.*, 1947). It is of interest that the myoepithelium responds to mechanical stimuli (Cross, 1954), and while this phenomenon is probably of little account in the normal removal of milk during suckling, it can be of diagnositic value in confirming the capacity of the effector tissue to eject milk. Animal experiments have shown that both central and peripheral disturbances of milk ejection occur in emotional distress (Cross, 1955*c*). The mechanisms are illustrated in Fig. 1B and involve both a central inhibition of oxytocin release and more rarely a peripheral block due to a sympathetico-adrenal discharge from the hypothalamus resulting in mammary vasoconstriction.

It is evident that continued non-removal of milk, whether due to absence of suckling or to a disturbance of the milk-ejection mechanism must lead to engorgement of the mammary gland with milk and eventual failure of secretion. To obtain more information about the early effects of mammary engorgement, experiments have been carried out on lactating rats (Silver, 1956). Fig. 1C illustrates the general conclusions from this investigation. Post-

partum engorgement was imitated experimentally in rats by subcutaneous ligation of the teat ducts of a number of the glands (the remainder serving as controls) on the day after parturition, and the animals were then allowed to continue nursing their litters. Tied glands became obviously distended in about eight hours and the enlargement appeared to be maximal at twenty-four hours. At this stage, if the ligatures were loosened or the teats cut off under anæsthesia, ejection of milk could be elicited by intravenous injection of 5–10 mU oxytocin. Histological examination showed the alveoli to be greatly distended but they were surrounded by an extensive capillary network which was full of blood. When engorgement was allowed to continue for forty-eight hours dramatic changes occurred both in the appearance and the responsiveness of the glands. They had become a dull white colour in marked contrast to the pinkish hue of normal glands. Histological study revealed that the capillary bed had collapsed and was almost devoid of blood cells. At this stage intravenous injection of 5–10 mU oxytocin no longer produced milk ejection. That this failure to eject milk was due to the reduced capillary circulation rather than to myoepithelial incompetence was shown by the fact that as little as 0·001 mU oxytocin evoked a local contraction response when applied directly to the exposed surface of the gland. Other changes observed in glands engorged for forty-eight hours or more included vacuolation of the alveolar secretory cells which later showed progressive thinning, while the contained milk became thicker in consistency.

The mechanism of closure of the mammary capillary bed in engorged glands is still the subject of study. It seems not to be the result of active constriction of the arterioles since these vessels appear unchanged in histological sections; moreover the sympatholytic drug 7337 ("Regitine" Ciba) does not restore capillary patency. It is possible that some substance in the retained milk exerts a direct constrictor effect on the capillaries. Observations on the changes occurring in the glands of rats whose litters have been removed show that the capillaries remain constricted until almost all the milk residue has been resorbed from the alveolar lumina. Shrinkage of the alveoli occurs before this time, so it appears unlikely that the capillary closure is wholly due to passive occlusion arising from the alveolar distension.

Whether a constriction of the alveolar capillary bed develops in naturally occurring cases of mammary engorgement is uncertain. However, Pickles (1953) obtained evidence of a reduction in mammary blood flow in primary engorgement of the human breast, and Waller (1952) reported that in such cases posterior pituitary injections often failed to produce milk ejection. The latter finding accords with experience of the comparable condition occurring in pigs. It would seem advisable to commence treatment early, and to use oxytocic extract in preference to whole posterior pituitary extract since the vasopressin content of the latter would intensify mammary vasoconstriction.

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Trembling in Newborn Pigs

By R. F. W. Goodwin, M.A., Ph.D., B.Sc., M.R.C.V.S., and A. C. Palmer, B.A., M.R.C.V.S.

Dr. Goodwin introduced the film with a few remarks about veterinary pædiatrics followed by some comments on the clinical condition of trembling. It was explained that many millions of farm animals were born annually and that the neonatal mortality and morbidity among them was extensive. Thus of the several million pigs born each year, about one-fifth did not survive beyond 8 weeks of age. It was important, therefore, for

economic reasons alone to study the diseases of young animals. More interesting, however, were the fundamental problems posed by these diseases and in their solution human pædiatrics and comparative medicine would undoubtedly benefit.

The condition of trembling in newborn pigs was not uncommon. Nothing was known of its ætiology and it was hoped that the film of the condition might prompt suggestions for further investigations. Dr. Goodwin believed after carrying out selective matings that the disease was not hereditary.

The film then followed and Mr. Palmer pointed out the main clinical features of the disease. The trembling, the result of severe tremor, was present at birth and affected the muscles of the head and limbs but not the muscles innervated by the cranial nerves. Providing the pigs could suckle, recovery followed and was usually complete within four to eight weeks. When the pigs were resting the tremor disappeared.

During the discussion that followed it was explained that neuropathological investigations were incomplete. So far only the nerve cells had been examined and these appeared to be normal.

A discussion took place during which there were many requests for further clinical information and many suggestions were made as to a possible diagnosis. It seemed apparent, however, that trying to match this clinical picture with one of the known nervous disorders of infants could not solve the problem of these pigs.

Experimental Hydrocephalus

By James W. Millen, M.D., D.Sc.

Anatomy School, University of Cambridge

Dr. J. W. Millen began by reviewing the methods used by other workers in the experimental production of hydrocephalus. The experimental procedure which causes hydrocephalus must operate in one of three ways: (1) by causing an increased production of cerebrospinal fluid, (2) by hindering the free circulation of the fluid, or (3) by interfering with its absorption. Unfortunately in many experimental methods known to cause hydrocephalus the actual mechanism by which the disease is produced is uncertain. He then gave an account of work carried out in the Anatomy School, Cambridge, on the production of hydrocephalus by maternal hypovitaminosis-A of which the following is a shortened version.

Over-production of cerebrospinal fluid.—One of the earliest attempts to produce experimental hydrocephalus by an increased production of cerebrospinal fluid was made by Dandy (1919). His experiments were based on the argument that occlusion of the great cerebral vein of Galen, which receives most of the venous return from the choroid plexuses of the lateral and third ventricles, should produce a congestion of the plexuses and lead to an increased production of fluid. Dandy succeeded in producing hydrocephalus in one dog out of ten in which the vein was occluded with a clip. Later attempts, however, by Bedford (1934) and by Schlesinger (1940) to repeat Dandy's experiments in dogs and monkeys were unsuccessful and these investigators attributed their failure to the efficiency of the collateral venous circulation. The work of Bedford and Schlesinger did not prove that a venous congestion of the choroid plexuses might not give rise to a hydrocephalus through an increased formation of cerebrospinal fluid but simply that such congestion could not be produced by occlusion of the great cerebral vein.

Three years ago, with the assistance of a generous grant from the Nuffield Foundation, Dr. Woollam and I began an investigation into the occurrence of hydrocephalus in the young of female rabbits subjected to a severe deficiency of vitamin A. The results of this work, up to the present, suggest that the underlying mechanism responsible for the hydrocephalus in these animals may be an excessive formation of cerebrospinal fluid, and this view is supported by the reported results of vitamin-A-deficiency experiments in farm animals. One of the most interesting aspects of this work has been that the deficient regime has been instituted not in the young or in the mothers after the beginning of pregnancy but a relatively long time before conception.

In order to obviate the possibility of a genetic factor inherent in an inbred strain, female rabbits were bought at intervals from accredited dealers and placed on a diet deficient in vitamin A but nutritionally adequate in every other respect. On this diet the rabbits remained in good health except for the occurrence of xerophthalmia in some animals. After periods ranging from twelve to twenty-eight weeks on the deficient diet the rabbits were mated with normal males. During pregnancy and until weaning the mothers and young were maintained on the same diet.

Since the colony was established 303 young have been born to deficient rabbits in first, second and third litters. Of these 242 were hydrocephalic, 52 normal, and 9 are still alive (Fig. 1).

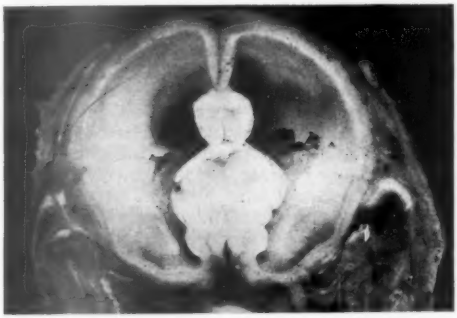

FIG. 1.—Coronal section through the head of a hydrocephalic rabbit, aged 7 weeks, to show the gross dilatation of the ventricles. ×1·4.

In the beginning the diagnosis of hydrocephalus during life presented a problem but after the examination of many litters it was found that the persistence of an anterior fontanelle in the week-old rabbit was indicative of hydrocephalus. In the normal newborn rabbit the anterior fontanelle is always closed. Radiological examination of the skull during the third week after birth revealed a characteristic doming of the skull with thinning of the calvaria and confirmed the diagnosis. Recently Dr. Dickson and I have made ventriculograms on a number of deficient young from 1–3 weeks of age and these have enabled the size of the dilated ventricular cavities to be assessed (Fig. 2).

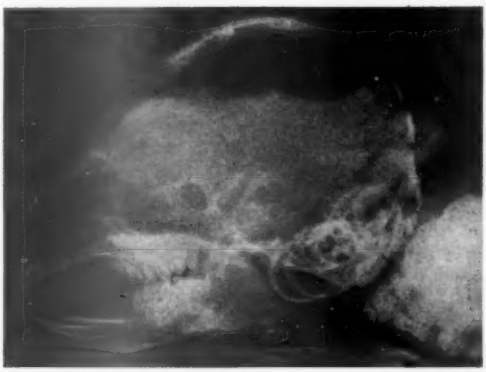

FIG. 2.—Ventriculogram of hydrocephalic rabbit, aged 13 days. ×1·4.

In the first litters it was found that the incidence of hydrocephalic young increased considerably when the mothers had been on the vitamin-A-deficient diet for twenty-four to twenty-eight weeks before mating. There was also an increase in the number of stillborn hydrocephalic young. In second and subsequent litters after still longer periods on the deficient diet almost all the young were hydrocephalic and many were stillborn or died within the first forty-eight hours after birth (Millen and Woollam, 1956). Live-born hydrocephalic young maintained on the same diet as the mothers usually died within one to three weeks but occasionally longer survivals, up to forty days were recorded.

After careful investigation the conclusion has been reached that the hydrocephalus produced in these animals by maternal vitamin-A-deficiency is probably due to an overproduction of cerebrospinal fluid by the choroid plexuses. This view of the mechanism responsible for the condition is not in conformity with the generally accepted hypothesis which ascribes the lesions of the central nervous system in hypovitaminosis-A, including hydrocephalus, to some form of disorganization of bone growth resulting in direct compression of the nervous tissues (Mellanby, 1938).

In the young hydrocephalic rabbits produced in this laboratory no signs of bony compression have been found. On the contrary there was, as has already been noted, a delay in

the closure of the anterior fontanelle and a gross expansion of the calvaria. Furthermore in these animals there was a herniation of the cerebellum through the foramen magnum. It is unlikely that such a displacement could occur if, as has been suggested, the hind-brain was compressed by the surrounding bone before ventricular dilatation occurred.

Another possible cause of the condition appeared to be an obstruction of the aqueduct and this was at first thought to be the underlying pathology. Subsequent histological examination of serial sections through the whole length of the aqueduct showed that, whilst the lumen of the aqueduct was distorted, its size, which at its narrowest part is about 0·04 sq. mm. in the newborn rabbit, was not significantly less in the hydrocephalic than in the normal animals. Intraventricular injection of carbon before death has also been carried out in several hydrocephalic animals. In some the carbon has failed to pass through the aqueduct, probably because of debris, but in others the carbon passed freely through the aqueduct into the fourth ventricle and thence into the general subarachnoid space.

If an increased production of cerebrospinal fluid was responsible for the hydrocephalus it seemed likely that a rise in the cerebrospinal fluid pressure might be the first indication of the presence of a vitamin-A-deficiency and might precede the appearance of hydrocephalus. Accordingly attention was turned to surviving young, which had been provisionally termed normal, from mothers on short periods of deficiency. Cerebrospinal fluid pressures in these animals were measured by cisternal puncture and it was found that the cerebrospinal fluid pressures were considerably increased, although the subsequent autopsy did not reveal any detectable dilatation of the ventricular cavities.

Further evidence in support of the hypothesis of an over-production of fluid has been provided by a recent series of experiments which I have been carrying out in collaboration with Dr. Dickson on the effect of giving vitamin A by mouth to young hydrocephalic animals. These experiments are in progress and whilst the results up to the present are suggestive further investigations will be needed before they can be considered conclusive. It had been found earlier that survival of the hydrocephalic animals could be considerably prolonged if vitamin A was given at 2 to 3 weeks of age. One grossly hydrocephalic animal was kept alive for five and a half months, during which time a considerable remodelling of the domed skull took place. He was finally killed only because paralysis of the limbs made it difficult for the animal to feed and look after itself. In the present work intraventricular pressures have been measured at the beginning of the experiment, usually in association with the injection of air for ventriculography, and at intervals of approximately one week. Immediately following the initial measurement vitamin A has been given. Subsequent measurements have shown consistent falls in the cerebrospinal fluid pressures. Depending upon the pressure level at the start of treatment pressures within normal limits have been reached usually within three to four weeks. It is difficult to suppose that these rapid falls in pressure could occur if the cause of the hydrocephalus was compression by the overgrowth of bone or was due to a true aqueductal stenosis.

In this brief review of experimental hydrocephalus greater prominence, than is perhaps justified, has been given to vitamin-A deficiency studies because this aspect of experimental hydrocephalus has been of particular interest to the author and his colleagues. Furthermore it may serve to draw attention to the possibility that the occurrence of hydrocephalus in an infant may be related to a hypovitaminosis in the child or in the mother.

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Section of Physical Medicine

President—J. SHULMAN, L.I.B., Ch.B.

[*February* 8, 1956]

DISCUSSION: AFFECTIONS OF THE TEMPOROMANDIBULAR JOINT

Mr. George T. Hankey (Senior Dental Surgeon to St. Bartholomew's Hospital, London; Dental Surgeon to The London Hospital, and Dental School, London):

Affections the Result of Trauma, Malocclusion and Muscular Imbalance

INTRODUCTION

The commonest complaints which affect the temporomandibular joint are those which are the result of trauma and muscular tension or trismus. In a previous paper (Hankey, 1954) I used the term "Arthrosis" as a convenient description of this group of disorders.

There seems to be a state of affairs which exists clinically before positive evidence of a degenerative or osteoarthritic condition of the joint can be substantiated and which, if treated from the correct ætiological basis, in the vast majority of cases can be cured. Bauer (1940) has described in detail the degenerative changes which take place in the temporomandibular joint, while Bennett (1948) and others have claimed that these changes in otherwise healthy joints can be seen as early as the second decade of life—from which it can be inferred that even normal functional stresses may lead to damage of the articular cartilage because of lack of blood vessels in this tissue which depends for its nutriment on the synovial fluid, and that some damage to the temporomandibular joint can occur in persons with normal musculature and occlusion.

In the case of the temporomandibular joint its movements, position and stresses are dependent not only on the musculature, but also on the relations of the upper and lower teeth through which the greater part of the load is normally transmitted from the mandible to the skull. It has been traditional to describe the mandible as a lever of the third class—the power between the fulcrum and the resistance—and according to a formula by Craddock (1951) the strain on the joint is at least doubled if the crushing force in the act of mastication is moved forward from the molars to the incisor teeth. Sicher (1947) and Robinson (1946) have shown that the type of tissue in the joint is not that which is usually associated with stress-bearing joints, while Wilson (1925) pointed out that the nutrient artery generally enters a bone in the area of least movement—indicating that in the case of the mandible the fulcrum is in the ramus near the lingula and not at the condyle. Robinson (1946) argues the theory of a non-lever action of the mandible, and the electromyographic analysis of the muscles of mastication by Moyers (1950) supports this theory. Moyers considers that the direction of the muscle pull, the sequence of contractions and the action of synergists all show that the resultant force is in the denture and that there can be no lever action when the resistance is directly in line with the resultant of the applied force. *The teeth and their supporting structures bear the heavy stresses for which they are designed and the joint is normally free of heavy strain. It follows that any deviation from the normal in occlusion or muscular physiology, which may upset the nice balance as between the two joints of the mandible and the skull, may have a damaging influence on the articular components.* This has, in fact, been found to be the case and the success of conservative treatment has been achieved by restoring that equilibrium as nearly as possible.

A detailed description of the anatomy of the temporomandibular joint and of the muscles of mastication can be found in the publications of Sicher (1952), Shapiro (1947), Sarnat (1951) and others, but a few points of special interest may be helpful.

ANATOMICAL AND HISTOLOGICAL NOTES

The temporomandibular joint is (Sicher, 1951) "the articulation between the mandible and the cranium. It is a highly-specialized joint and distinguished from most others by the fact that the articulating surfaces are *not* covered by hyaline cartilage but by an avascular fibrous tissue which only sometimes contains a few cartilage cells. The movements of the mandible are restricted because of its bilateral articulation with the cranium so that the right and left joints are coupled together. It is a complex joint because a disc or meniscus is interposed between the temporal bone and the mandibular condyle, dividing the articular space into an upper and lower compartment; in the upper compartment gliding or translatory movements of the meniscus on the temporal bone take place, while in the lower compartment there is an eccentric hinge movement of the condylar head in relation to the meniscus. The temporomandibular joint can best be described as a hinge joint with a movable socket".

The only ligaments of the joint of importance are the capsular and the lateral or temporomandibular (Fig. 1). *The lateral ligament* is a dense collagenous thickening of the capsule on the lateral side of the joint passing downwards and backwards from the root of the zygoma above to the neck of the condyle below and behind. It is normally taut in all positions of the joint and serves to keep the condyle, disc, and temporal bone firmly opposed and to prevent backward displacement of the condyle.

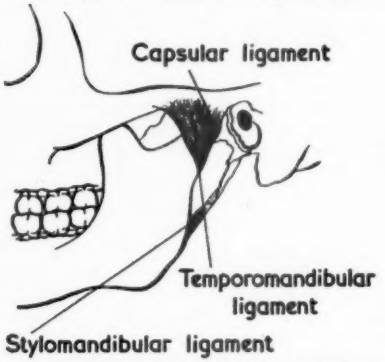


FIG. 1.—Drawing—lateral view—to show the two main ligaments of the temporomandibular joint. (The stylomandibular ligament is accessory to the joint and helps to prevent backward displacement of the condyle.)

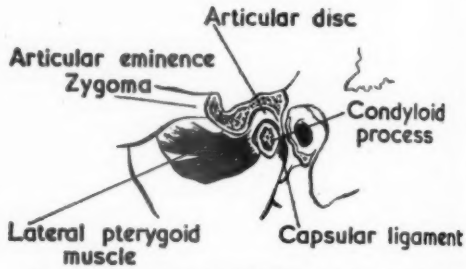


FIG. 2.—Drawing—lateral view—to show the insertion of the fibres of the upper head of the lateral pterygoid muscle into the anterior edge of the disc, while the fibres of the lower head are inserted directly into the anterior surface of the neck of the condyle.

The capsule between the margins of the articular surface of the temporal bone and the circumference of the disc is very loose to allow extensive gliding movement in the upper compartment of the joint. The capsular fibres below the disc are short and tight and are almost immediately inserted into the neck of the condyle, binding and closely conforming the disc to it—except in front where they are weak and loose so that a forward dislocation can easily occur. An injection into the upper joint space is thus very much easier to accomplish than into the lower. The posterior wall of the capsule is inseparably blended with the vascular posterior attachment of the disc and its fibres are only distinguished because they run directly downwards from the temporal bone to the neck of the condyle behind.

The lateral pterygoid muscle (Fig. 2) is inserted into the anterior wall of the capsule and anterior edge of the disc by some of the fibres of its upper head. The rest of the muscle is inserted directly into the anterior surface of the neck of the condyle below the joint. The upper head is thus capable of exerting an antero-medial traction on the disc while the rest of the muscle pulls directly on the mandible; this arrangement serves as a balancing fixation for the disc and prevents it slipping backwards when the jaws are closed forcibly on food between the teeth. According to Rees (1954) a few of the deep fibres of the masseter may blend with the antero-lateral aspect of the capsule and meniscus and thus counteract the medial pull of the pterygoid. He also describes in detail a new conception of the relations of the condyle, disc and temporal bone in the act of normal opening of the mouth.

A photomicrograph of a sagittal section of the joint of a child aged 3 years (Fig. 3) shows the outlines of the joint cavities, the disc in between the condyle and the eminentia, the muscle fibres attached to the anterior ridge of the disc, the thin intermediate or central portion of the disc and the thick posterior ridge or dome of the disc fitting up into the glenoid fossa. The disc behind splits into two layers; a thick upper layer of loose vascular and elastic tissue attached to the posterior margin of the temporal bone and blending with the posterior capsular fibres, and a thin lower layer of dense collagenous fibres, similar to the main body of the disc, continued downwards behind and attached to the neck of the condyle. The articular surfaces of the condyle and eminentia are covered with a layer of fibrous tissue which is *not* continued up into the depth of the fossa, where the bone separating the joint from the brain is thin and not meant to resist pressure. The growth centre of the condylar head is a thin layer of hyaline cartilage between the fibrous covering and the bone; after normal cessation of growth this cartilage still persists, but in a gradually decreasing amount, and is of importance for the explanation of growth anomalies.

The meniscus itself is composed of interlacing bundles of thick collagen fibres which on the surface run parallel to it. The centre of the disc is bloodless, but the periphery has a good

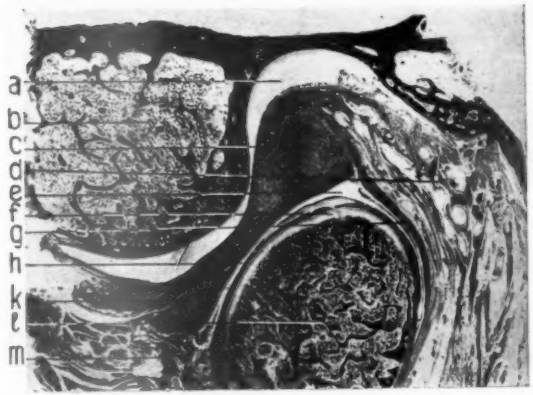


FIG. 3.—Photomicrograph of a sagittal section through the left temporomandibular joint of a child aged 3 years. Stained hæmatoxylin and eosin. ×4. a, upper joint cavity and glenoid fossa. b, cancellous bone of eminentia. c, posterior thick ridge of disc. d, loose vascular connective and elastic tissue attaching posterior ridge of disc to temporal bone and posterior wall of capsule. e, lower joint cavity. f, hyaline cartilage—the condylar growth centre. g, thin collagenous posterior downward prolongation of disc inserted into neck of condyle behind. h, fibrous tissue layer covering articular surfaces of eminentia and condyle. k, anterior ridge of disc. l, cancellous bone of condyle. m, fibres of lateral pterygoid muscle.

blood supply especially from the posterior attachment. Le Gros Clark (1946) and Robinson (1946) believe that menisca are capable of repair, but Sprinz (1954) considers this most unlikely in the case of the temporomandibular joint. It is probably true that the bloodless centre portion, if torn or perforated will *not* repair; but it seems likely that an injury or tear of the peripheral attachment *can* heal if rested, thus accounting for the many cases of temporary derangement which recover. Elastic fibres are present in considerable quantity in the loose upper layer of the posterior attachment of the disc and a few can also be found in the disc itself of a young person.

The nerve supply of the joint is through twigs from the auriculo-temporal branch of the third division of the V nerve which enter the capsule from behind; sometimes masseteric twigs also enter laterally. The auriculo-temporal nerve itself is well below the attachments of the capsule and *cannot be compressed* against the tympanic plate by a retruded condyle.

The blood supply is by small vessels from the superficial temporal or internal maxillary branches of the external carotid, mostly entering the capsule behind.

A synovial membrane, as such, does *not* cover the articular surfaces, but in the loose fornices and peripheral boundaries of the joint cavities there is a cellular layer rich in cells and blood vessels and often thrown into folds or villi and it is from these cells that the synovial fluid is secreted and through which the avascular tissues of the joint receive their nutrition.

Backward pressure of the condyle on the posterior vascular attachment of the disc or fibrosis of the capsule will impair the vitality of the articulation and at the same time give rise to local or referred pain or reflex muscular spasm. According to Thonner (1952) such pressure can bear on a vessel, newly described by himself, from the internal maxillary artery to the cochlea and inner ear as it passes through the glaserian fissure and thereby account for the rare symptoms of deafness, tinnitus, or giddiness. Zimmerman (1951) has demonstrated that involvement of the chorda tympani, or erosion of the tympanic plate due to condylar pressure as claimed by Costen (1934) and Goodfriend (1947) are both wellnigh impossible; when tympanic erosion does occur it is usually due to the spread of infection from the ear.

While describing the signs, symptoms, ætiology and treatment of temporomandibular arthrosis, I will refer to my analysis of 150 cases seen in the five years prior to April 1953 and included in my Charles Tomes Lecture (Hankey, 1954).

SIGNS, SYMPTOMS, AND ÆTIOLOGY

Age and Sex Incidence

Women were affected three times as often as men. 57% developed symptoms from adolescence to age 30, during the years when the permanent teeth are erupting or are in position—on the other hand very few cases, only 4%, developed symptoms after age 50

when the edentulous state is more likely to have been reached—yet Costen's paper (1934) concerned edentulous patients almost exclusively.

Time Before Seeking Treatment

Most of the patients sought treatment within six months of the onset of symptoms, but only 6% within a few days, indicating that very few have severe initial symptoms.

Symptoms.—Unilateral or bilateral clicking in the joint without pain was the most frequent complaint, accounting for 30% of the cases, while 27% had a click associated with pain. The remaining 43% had never clicked and had a wide variety of other symptoms mostly confined to the immediate region of the joint. Pain, usually brought on by movement, mastication or opening wide, was in the joint, up the auriculo-temporal nerve or along the second or third divisions of the V nerve. The pain would be momentary, sharp and stabbing, or a steady dull kind of neuralgia or a gnawing soreness of the joint. Only very few, 9 in all, complained of deafness, tinnitus, lingual or other symptoms made so much of by Costen. Besides pain, the main complaints were some kind of interference with free movement of the jaw—limited opening, occasional locking or recurrent subluxation. Stiffness of the jaw on waking in the morning was common. Headache, neckache or difficulty in swallowing were rare symptoms. 23 *cases complained of V nerve neuralgia without any other symptoms and it is these cases which present the greatest difficulty in diagnosis and whose basic ætiology may be overlooked.*

Mode of Onset and Cause of Symptoms

37% of the cases started suddenly; the remainder had a gradual onset. Only 20% could be attributed to extrinsic injury; the remainder were due to intrinsic traumata.

Extrinsic traumata were more common in men and were direct or axial. A direct blow on the side of the face in the region of the joint or an axial blow on the chin, besides causing injury at the point of impact may result in synovitis, torn ligaments, or a fractured condyle.

If the teeth are apart at the moment of impact, the lateral pterygoid tenses to take the strain and the fibres of the upper head may dislodge the disc antero-medially in relation to the condyle or else may tear away from the disc so that the latter tends to drift distally in the joint. An anterior displacement of the disc will cause obstruction to forward gliding of the condyle with limited opening; distal displacement will prevent full closure of the teeth on the same side.

The lateral wrenching employed in the extraction of lower molars may strain the joint ligaments, giving immediate pain in the conscious patient with subsequent symptoms of derangement which can be traced to this event. A true anterior dislocation of the condyle from any cause may rupture the capsular ligament at the same time and cause an effusion into the joint.

Pain in and around the joint, probably accompanied by local swelling, tenderness and restriction of movement will be the immediate symptoms of all extrinsic traumata.

Intrinsic traumata are self-inflicted. Sometimes the onset of symptoms in the joint can be clearly connected by the patient with an incident such as yawning, laughing or eating. There is a sudden sharp pain in the joint as if something is nipped—maybe the disc caught momentarily out of place or a synovial fold drawn in and pinched, as in the knee-joint. The sharp pain may be followed by the feeling of something in the way preventing full movement and often self-manipulation restores normal function on the first few occasions, but the joint remains stiff and tender for some days indicating a synovitis. If the jaw can be rested at this stage repair can take place; this should be immediately followed by correction of any occlusal deformity. If neglected, repeated intrinsic traumata set up degenerative changes in the joint with stretching of the capsule, clicking, and loosening of the conformity of the disc to the condyle.

In others, for a varying length of time, there will have been a regular or intermittent click on movement, with or without pain, but unconnected in the first place with a special incident until one day the click suddenly stops. It is then found that the mouth can only be partly opened—usually described by the patient as "dislocated" or "out" and that the joint is extremely painful on trying to force it wider; there may, in addition, be considerable muscle spasm which in itself is painful. The inability to open indicates that a misplaced disc is obstructing forward movement of the condyle. The good joint then over-extends to compensate for the fixed side which may gradually become painless although still fixed; later still pain commences in the over-mobile joint due to capsular stretching, subluxation and muscular imbalance. If the patient is first seen at this stage it may be difficult to decide which joint is the real culprit.

Sometimes symptoms commence after relaxation of the jaw in sleep or through lying with the head turned at an acute angle. Prolonged mouth-opening for conservative dental treatment is very tiring and causes muscular cramp. Anything which upsets the delicate muscle balance between the two joints may initiate symptoms; trismus, either reflex or

mechanical, is a common cause and the underlying factor in 20 cases was an erupting or impacted third molar or carious tooth. A pericoronitis or painful tooth necessitates an eccentric bite of accommodation in order to avoid the tender spot and the eccentric bite in turn forces an asymmetrical placing of the condyles in their fossæ, with unnatural strains on the components of the joints.

But the cumulative effect of altered stresses and strains imposed by malocclusion, loss of vertical dimension or loss of molar support is the most frequent ætiological factor which initiates degenerative changes in the joint. How do these occlusal deformities affect the function of the joints?

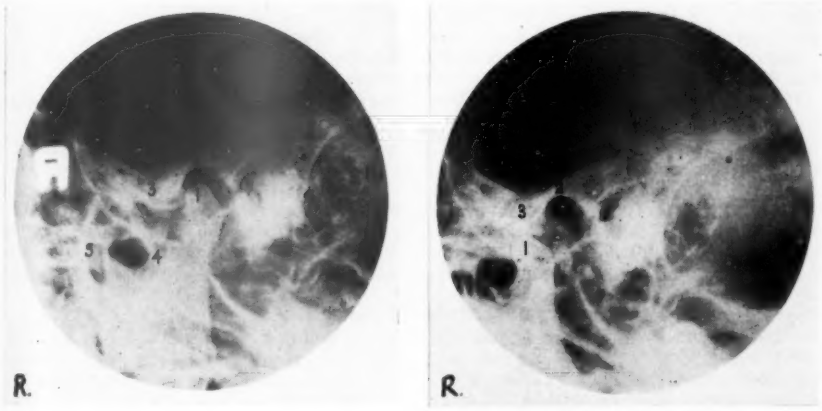
The Ætiology of Injury due to Malocclusion

The primary function of the mandible is mastication and, in the act of mastication or crushing of the food, as has already been emphasized, the main weight or force is transmitted through the teeth to the maxilla and cranium and only in part to the joints—that is if there is a full dentition in normal occlusion.

The normal symmetrically developed mandible, complete with its dentition and musculature, starts all movements of mastication and speech from a position of rest which is constant for any one person, but may alter in the presence of tension or disease.

The rest position is fixed by the tonus of the elevator and depressor groups of muscles which, when relaxed, allow the mandible to drop slightly. The teeth are then slightly apart and the space between them, which does not normally measure more than 4 mm., is termed the *Free-way space*; if it measures 5 or more millimetres the free-way space is said to be increased and there is probable overclosure of the bite.

In the position of rest the mandible, as judged by the point of the chin, is balanced centrically in mid-line. If *lateral oblique radiographs are now taken* of the temporomandibular joints both condyles appear symmetrically poised half-way up the posterior slopes of the eminentiæ, with more joint space above and behind than above and in front (Fig. 4). From



A B

FIG. 4.—Lateral oblique radiographs of the normal temporomandibular joint. A, closed or at rest. B, open.

1. Head of condyle. 2. Glenoid fossa. 3. Eminentia. 4. Sigmoid notch. 5. Coronoid process. 6. Mastoid air cells. 7. Auditory canal.

the rest position to *normal functional occlusion* of the teeth the mandible should close centrically by a hinge movement in the lower compartments of the joints without any deviation or gliding, so that all the teeth meet with equal pressure at one and the same time, and, by interlocking of the cusps, prevent further upward and backward movement of the condyles (Thompson, 1949); yet although locked against further backward displacement, the cusps should be capable of *free lateral grinding movements* while still remaining in contact. The ability to chew as well as to bite is of great importance and it will be found on trial that many occlusions are *locked against lateral grinding*. Rectification of this fault alone will ease the strain on many joints.

The teeth of the two jaws can be compared with the teeth of two cogs which are designed to interdigitate exactly: any maladjustment of apposition and the two cogs will wear away where they first hit, or will jam, or will glide into full contact only if the axis of one is adjust-

able in relation to the other. If radiographs of the joints are repeated with the teeth in normal centric occlusion and compared with those of the mandible at rest, there should be very little difference; the condyles may have travelled upwards slightly, but they should still be symmetrically placed and the joint spaces should still be greater above and behind than above and in front (Lindblom, 1953). Any disparity suggests that the cogs or teeth are meeting out of true and that the adjustment has had to be taken up in the joints, imposing an unusual strain upon them and liable to produce pain.

If certain cusps meet prematurely (Fig. 5) they may act as inclined planes and force the

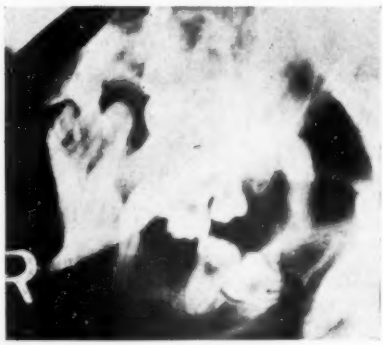
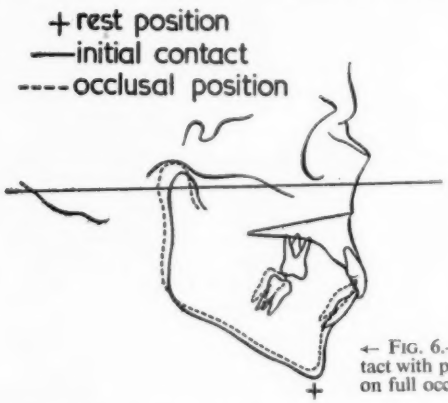


FIG. 5.—Radiograph of premature contact of $\underline{7}|$ with $\underline{7}|$ resulting in posterior displacement of the condyle on the same side.

mandible into a *lateral deviation or eccentric occlusion*; the whole jaw will then be rotated horizontally and radiographs of the joints will show asymmetrically placed condyles—one more deeply placed and retruded in its fossa than the other, which will be normally placed or slightly advanced. *Bilateral backward displacement of the mandible and condyles* will ensue if there is initial contact of the lower incisors with the palatal surfaces of the uppers—as in Angle's Class II Division II type of occlusion (Fig. 6). In radiographs of such a case



← FIG. 6.—Diagram of initial incisal contact with posterior displacement of condyle on full occlusion (J. R. Thompson, 1951).

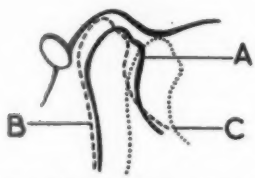


FIG. 7.—Diagram of temporomandibular joint with the condyle in positions of A, rest, B, backward and upward displacement in abnormal occlusion, and C, open mouth.

both condyles will be retruded in their fossæ as compared with the rest position. The condyles will be similarly displaced if there is *overclosure of the bite* with loss of vertical dimension; this ensues if molar teeth have been extracted and there is lack of molar support, or if the molar occlusion has drifted and collapsed following the extraction of a tooth here and there, or if there has been marked attrition of the occlusal surfaces of the teeth from wear and tear, or if tissue-borne artificial dentures have sunk following the absorption of the alveolus beneath them.

Bruxism or habitual clenching and grinding of the teeth is often a sign of an emotional disturbance or anxiety. Due to an hypertonic state of the elevator muscles the teeth are worn away and overclosure of the bite ensues; but more important, as reported by Copland (1954), the rest position is almost permanently abolished so that the joints and muscles are always under tension and become painful for this reason alone.

The Production of the Click

In overclosure, lateral deviation, or backward displacement of the mandible, the condyle travels farther up and back in the fossa than at rest (Fig. 7). By assuming that the disc is held at the position of rest by the upper head of the lateral pterygoid muscle, it is reasoned that every time the teeth meet in an abnormal occlusion of this type the condyle tends to slip posterior to the disc and the disc becomes progressively looser in its attachment to the head. A click is heard at the commencement of opening as the head slips over the thick posterior ridge of the disc and re-engages with it and often a second click is heard towards the end of wide opening as the head slips beyond the anterior ridge of the disc on to the anterior slope of the eminentia, the disc itself being prevented from travelling farther forward by the limited stretch of its temporal attachment behind. Sooner or later re-engagement fails, the disc remains anterior (or posterior) to the head and locking and pain ensue.

As a diagnostic point if there is clicking of the joint and overclosure is suspected, ask the patient, after clicking, to close on the thin handle or blade of a knife placed between the back molars. This will prevent the overclosure and on opening from this new starting point the click may be abolished. In such cases the prognosis of a cure by a bite-opening splint or prosthesis is almost assured.

Pain of Obscure Origin. Costen's Syndrome

There remains the group of patients who complain only of pain or other sensory changes. The ætiology and differential diagnosis of facial pain were recently reviewed by Stones (1956). Among the large number of possibilities, pain originating from changes in the mechanism of the temporomandibular joint or from imbalance of the muscles of mastication as the result of occlusal deformities or reflex trismus should always be considered.

The syndrome of symptoms described by Costen (1934, 1936, 1944) is:

Neuralgia of the second or third divisions of the V nerve.
Pain in and around the ears.
Stuffy sensation in the ears.
Pain up the back of the head and down the side of the neck.
Headaches.
Sinus pains.
Impaired hearing.
Tinnitus.
Altered sensation in the tongue and throat.

Costen accounted for these symptoms by the pressure of the retruded condyles in overclosure of the bite upon the chorda tympani, upon the eustachian tube, or upon the auriculo-temporal nerve, or by erosion of the tympanic plate or of the roof of the glenoid fossa. None of these postulates has been proved, although the symptoms can be real enough. The more likely explanation is that the pain or other sensory change is reflex or referred from the joint due to the pressure of the retruded condyle upon the nerves or vascular tissues in the posterior part of the fossa and to the subsequent degenerative changes taking place. Suffice it to say that the vast majority of cases will be cured or relieved by restoring the faulty occlusion to normal, thereby preventing condylar retrusion. In my analysis, the first two symptoms were fairly common, but the remainder were rare, especially deafness, and tinnitus. Harvey (1948) in his observations on otitic barotrauma in airmen, found no relation between overclosure and pressure on the eustachian tubes; and Ireland (1951) states that in his series the only cases with auditory symptoms were undoubted examples of otosclerosis. Campbell (1955), after the exclusion of all other causes, considers that mandibular displacement as the result of malocclusion can be the cause of obscure facial pain, but that the pain is also dependent upon the muscular tonus, the threshold of the individual to pain and upon psychological factors.

Investigations

The two most important investigations—bite analysis and joint radiography—are both open to misinterpretation owing to variable techniques. Analysis of the bite on the dentatus articulator calls for great accuracy, but the technique as described in detail and with diagrams by Trott and Wade (1955) should help to standardize this part of the work. A large number of X-ray films taken of the temporomandibular joint are often misleading; the anatomical and technical difficulties and means of surmounting them are clearly set forth by Craddock (1953). The trans-cranial lateral oblique view will suffice for most purposes; very rarely will an arthritis or gross pathology be disclosed; the purpose rather is to verify asymmetrical placing or abnormal movement of the condyles. If a planograph is thought necessary, the technique described by White *et al.* (1952) should be tried.

In all cases, where the radiograph is to be taken by a third party, if the rest position of the mandible is required it should be registered beforehand in a composition squash bite which can be placed between the teeth by the patient at the right moment. Lastly, the work of Nörgaard (1947) should be consulted for the technique of injecting the joint for any purpose.

Treatment

The treatment can now be outlined according to the ætiology of the complaint; it can be divided into prophylaxis, acute and chronic cases.

Prophylaxis.—A normal and well-developed dentition, kept in good order, will prevent the development of most cases of temporomandibular arthrosis due to intrinsic traumata. A much more comprehensive service for the treatment and conservation of children's teeth and for the orthodontic correction of occlusal deformities and immature muscle patterns or habits is needed. If a permanent or deciduous tooth does have to be extracted for other than orthodontic reasons, it should be replaced as soon as possible by a prosthesis or fixed bridge to prevent movement and tilting of the teeth either side of the gap and to prevent over-eruption of the unopposed tooth in the opposite jaw. In the adult, besides conserving the teeth and supporting tissues in good order, the functional occlusion should be kept centric and at the correct level by preventing loss of vertical height from any cause. If several teeth have to be extracted and a space is deemed too wide for a satisfactory bridge, then partial dentures should always be tooth-borne to prevent sinking and parodontal complications. In early cases of bruxism or habitual grinding of the teeth, the occlusal surfaces may have to be protected by inlays and an acrylic overlaid prosthesis worn at night to prevent further loss of vertical height. Patients with full artificial dentures should have them checked at regular intervals—even though comfortable—and kept at the correct occlusal height by relining them in order to counteract the inevitable sinking and loss of vertical dimension due to alveolar resorption.

Acute cases. (*a*) *Extrinsic causes* (12 cases).—These should be treated in the first instance according to first surgical principles. The part should be rested and, if possible, immobilized by intermaxillary wiring after reduction of any fracture or dislocation. When the signs of effusion and inflammation have resolved, movement and function must be gradually restored aided by physiotherapy and sometimes by a training flange if there is muscular resistance to centric opening. Later, the occlusion should be checked and restored if considered necessary.

(*b*) *Intrinsic causes* (43 cases).—Here, as previously explained, the cause is different. Owing to repeated traumata and unusual strain on the joint brought on by some form of malocclusion or muscular imbalance, the components are already lax and subject to further injury. Some trauma, of no account in the normal, causes acute pain, effusion and trismus. The part must obviously be rested in the same way as for an extrinsic injury, but if radiographs of the joint show a much retruded condyle *the backward displacement must first be reduced and prevented from relapsing* by opening the bite with some form of splint. The muscular spasm may be so severe that it is impossible to take satisfactory impressions without an anæsthetic; this difficulty must somehow be overcome because *rest with the condyle still retruded will do little good.* Immobilization, wearing a bite-opening splint, will have the quickest and most satisfactory result. Local injections of Xylocaine may help to relieve the pain. Later, when the spasm has relaxed, a full analysis of the bite must be made and the occlusion restored to normal.

If seen soon after the event, a misplaced disc can sometimes be reduced by manipulation under an anæsthetic; afterwards the mandible should be rested as just described. Sometimes, however, even after rest, the disc is so badly damaged or displaced that it is impossible to restore function without surgical intervention.

Chronic cases (17 extrinsic, 78 intrinsic causes).—(*a*) *Reflex trismus and muscle imbalance* causing a temporary derangement of the joint can often be traced to the pain or irritation of an erupting, carious or impacted tooth; removal of the cause may effect a speedy cure. In others the occlusion is such that orthodontic treatment is desirable; but in the effort to achieve a more regular arrangement of the teeth and an improved occlusion, the effect on the positions of the condyles in their fossæ should be checked. If the condyles are forced into a retruded position, ultimate derangement of the joint may ensue.

(*b*) *In overclosure and many Angle's Class II cases there is an initial incisor contact* because of lack of vertical growth of the alveolus supporting the molar teeth, so that the free-way space is increased and the mandible gradually forced backwards in full occlusion. In the majority of these cases probably no symptoms will develop; but if the molar height can be raised to the level of the initial incisor contact the condylar displacement will be prevented and the strain on the joints relieved. Staz (1951) claims to achieve this result by fitting an upper anterior bite block leaving the molars uncovered in the hope that they will erupt further and diminish the excessive free-way space; the block can then be discarded. This method is more likely to succeed in children during the active period of growth. In the adult the same effect is achieved by bringing the molar contact up to the level of the incisor contact by means of a prosthesis or splint which covers the occlusal surfaces of either the upper or lower molar teeth or, in extreme cases, of both. The splint

in the first place should always be made in acrylic (Fig. 8) for ease of adjustment; using the same or duplicate models on the Dentatus with the same measurements, the occlusion corrected by this first splint can later be accurately reproduced and maintained by a permanent and much less bulky metal prosthesis in gold (Fig. 9) or in chrome-cobalt (Fig. 10).

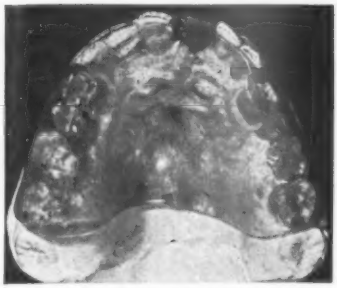


FIG. 8.—A temporary upper acrylic overlaid prosthesis.

FIG. 9.—A permanent skeleton gold and acrylic upper overlaid prosthesis.

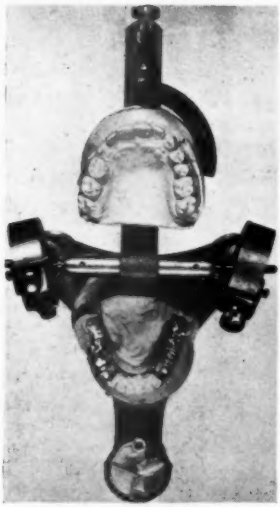


FIG. 10.—A permanent skeleton chrome-cobalt lower overlaid prosthesis; models mounted on the Dentatus.

In cases of overclosure due to loss of molar teeth or due to attrition the same procedure is adopted. In edentulous cases, already wearing full dentures, the excessive free-way space is first reduced by overlaying one or other denture with acrylic to the correct height and bite and worn until comfortable. Later the denture is remade to the new occlusion.

(*c*) *In premature contact* one or several cusps are meeting before the mandible has closed through the normal range from rest to occlusion. Careful study of models set up on the Dentatus articulator will disclose the points of interference which swing the mandible off centric occlusion and result in condylar displacement. Selective grinding of these points in the mouth will often be sufficient to restore centric occlusion and effect a cure of the arthrosis. Sometimes it will be necessary to remove the premature contact by extraction of the tooth or by replacing it with an artificial crown in correct occlusion. In others it may be possible to move the tooth by orthodontic measures.

(*d*) *In all cases of malocclusion* the aim is to restore the occlusion to the normal centric level and to maintain it in equilibrium so that the teeth can grind freely in all directions without locking, bumping or unequal strains. The condyles, which on X-ray were formerly retruded or asymmetrical in their fossæ in occlusion, should be re-positioned as near as possible to their normal resting positions when the teeth close naturally or on an appliance. When making the appliance the condylar position must be checked by a further X-ray (Fig. 11). *The whole purpose of the treatment is to prevent the condyles from being forced backwards and to keep them balanced and symmetrically placed in their fossæ.* Unless this is achieved the treatment will probably fail. But the appliance should never occupy the whole free-way space.

(*e*) *Training flanges* attached to cap splints had to be constructed in 6 cases to rehabilitate muscles which for a considerable period had become accustomed to a marked deviation to one side and were not accommodating themselves to centric opening by other means. Sometimes deliberate muscle exercises will achieve the same result without a training flange.

(*f*) *Injections into the joint* of various substances have been tried for mild degrees of osteo-arthritis or when pain or obstruction to movement is not being improved by bite rehabilitation. According to Rossing and Lutterbeck (1954) hyaluronidase injected into the peri-articular tissues

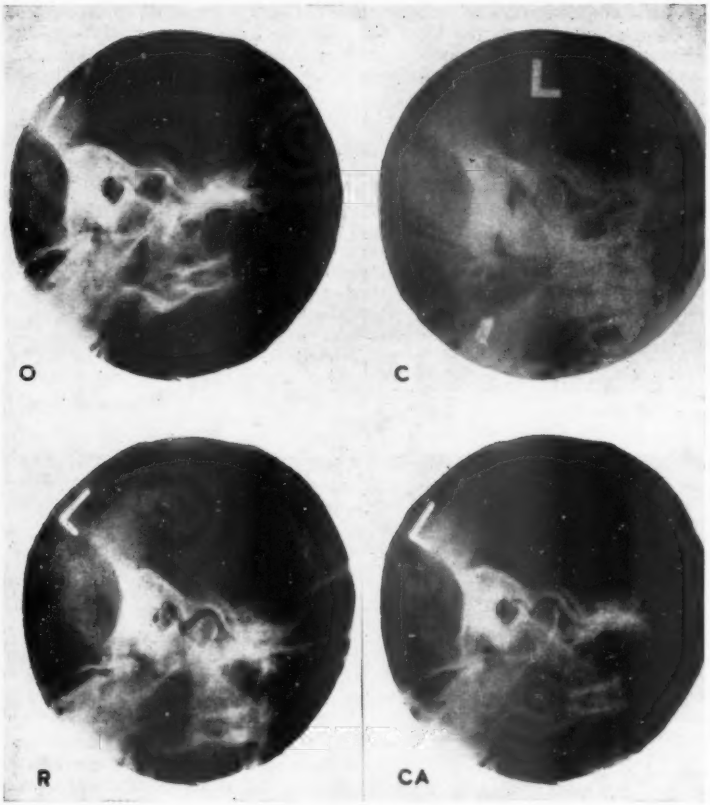


FIG. 11.—Radiographs of temporomandibular joint before and after correction of backward displacement of the condyle in malocclusion. C, closed. The condyle is retro-positioned in the fossa. O, open. There is limited forward movement of the condyle. R, resting. Compare with C; in normal occlusion the condyle does not move back from the resting position. CA, closed, wearing bite-opening appliance. The condylar position is corrected to that of R.

may facilitate the passage of fluids to and from a joint and thereby improve its nourishment. Hydrocortisone can be tried in the same way and sometimes gives relief. Occlusal deformities should still be corrected. For loose, recurrently subluxating joints various irritating substances, such as iodine, Lipiodol, or sodium psylliate (Archer, 1956) have been tried in order to set up irritation with resultant fibrous contraction of the capsule.

(*g*) ***Surgery*** is required in a decreasing percentage of cases. In this series, 20 cases had meniscectomy performed and 1 condylectomy. Some cases respond unfavourably to conservative treatment, namely those which are already almost completely jammed owing to meniscal damage. They continue to suffer severe local pain in spite of other treatment. Particularly is this so if the lateral pterygoid has torn away from the disc and the latter has drifted towards the back of the joint, preventing closure of the teeth. Meniscectomy will usually give immediate relief—but this does not absolve the surgeon from having the occlusion checked afterwards. For loose, recurrently subluxating joints some surgeons expose the capsule and plicate it or strengthen it laterally by turning down a strip of temporal fascia. Others insert a piece of bone in the anterior part of the joint to limit forward movement—the mere opening of the capsule will probably have the same result.

(*h*) ***Physiotherapy***, in the form of heat and muscle rehabilitation, is of great assistance in many cases. Besides its local effect, the patient, who in many instances is of an anxious disposition, feels that something active is being done and therefore gains confidence; the threshold for pain is correspondingly raised.

A few patients, with nothing but an occasional click, aggravate the condition by spontaneously repeating it; others wake up in the morning with a stiff jaw through lying with the head at an acute angle. One, a singer, subluxated his jaw repeatedly by opening his mouth too wide in order to gain a high note. Such patients, by self-restraint and change of habits, can cure their joint troubles themselves after advice.

Results (*First* 150 *Cases*)

When compiling the results of treatment of the first 150 cases, the percentages of successes were taken from the 125 completed cases; the remainder were still under treatment. 72% were cured, 20% were much better, and 8% were failures. 20 cases or 16% underwent surgery of the joint.

Table I—Results (*Second* 262 *Cases*)

Table I shows the results of treatment of my next series of 262 cases, which have not yet been otherwise analysed. Of the 190 completed cases, 170 (89%) were cured, 15 were improved and 5 (2·6%) were no better.

TABLE I.—RESULTS OF TREATMENT OF A FURTHER 262 CASES OF TEMPOROMANDIBULAR ARTHROSIS
April 1953–January 1956

Cured		
Resolved naturally	21	
By conservative measures		
Onlaid prosthesis, Cuspal grinding, Dentures, Immobilization	122	
Psychiatry	2	
Physiotherapy	2	
Training flange	1	
Joint injection	4	
By operation: Meniscectomy, Condylectomy, Tenotomy		
By operation and prosthesis	3	
By extraction of 8's or other teeth ..	15	
	—	170
Improved		
By conservative measures	12	
By operation	3	
	—	15
Failed		
By conservative measures	5	
By operation		
	—	5

Females ..	209	4 : 1	Number treated .. 190
Males ..	53		Still under treatment 46
	262		Did not return .. 26
			262

By comparison with the first 150 cases, it will be seen that the percentage of cures in the second series is 16% higher, and that only 6 cases (3%) required surgical treatment.

A film was then shown of the histories, models, radiographs, jaw movements and conservative treatment of 5 representative cases (*see* Hankey, 1954).

SUMMARY

(1) Certain details of the anatomy and histology of the temporomandibular joint are given.

(2) The ætiology, signs and symptoms of temporomandibular arthrosis are described, with references to a previous analysis of 150 cases (Hankey, 1954).

(3) The results of treatment of 150 cases previous to, and 262 cases since, April 1953, are analysed. It is clear that conservative treatment is successful in an average of 80% of cases. In the first series 16% were treated surgically, in the second series only 3%.

(4) The great majority of cases complained of some form of interference with the function of the joint, with or without pain. Only 16·6% of the first series of 150 cases complained of pain without reference to the joint; the syndrome described by Costen is discussed.

(5) Malocclusion in one form or another, with resultant condylar displacement, is the main factor in the causation of temporomandibular dysfunction.

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Figs. 1, 2, 3, 4, 6, 7, 11, have been reproduced from the *British Dental Journal* (Hankey, 1954), by kind permission.

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Professor C. F. Ballard (Orthodontic Department, Institute of Dental Surgery, London University):

An orthodontist is only concerned with those cases of temporomandibular joint dysfunction which are associated with mandibular displacement. It is likely that many cases have in the past been treated surgically and even as a last resort referred to a psychiatrist, because the displacement has not been detected. Only in recent years has the importance of displacement been appreciated.

In recent years it has become obvious from clinical experience that the mandible cannot be made to grow nor can its growth be controlled in order to improve its relationship to the maxilla. It has also become evident from clinical experience that the position of the alveolar structures, whether normal or abnormal, is the result of the morphology and behaviour of the lips, cheeks and tongue and the behaviour cannot be changed except in limited ways.

Efforts to change the posture and behaviour of the lips and tongue and to reposture the mandible have gone through the same phases as have similar efforts in the field of physical medicine. Thirty years and more ago, postural exercises were in vogue to improve tone in the facial muscles and in the case of the mandible improve the tone of the muscles which protrude the mandible in mandibular retrusion and vice versa in mandibular protrusion.

This approach produced no results. The next phase was an attempt to re-educate: by conscious appreciation of the new posture required, and by reflex re-education. This approach has also failed, for obvious reasons.

These facts led to a fuller investigation firstly on the clinical side, into mandibular posture and movement and secondly into the biological background of posture and behaviour.

As a result, the author put forward the following hypotheses on oro-facial behaviour.

(1) That the posture of the mandible is endogenously determined and is not simply the result of the reciprocal postural tonus of depressors and elevators.

(2) That the occlusal level is reflexly established: the proprioceptive nerve endings in the supporting structures of the teeth reflexly limiting the activity of the muscles of closure.

(3) Masticatory patterns of activity [basic co-ordinating patterns (Weiss, 1941)] are endogenous in origin at levels well below the conscious level in the central nervous system.

(4) The teeth in the dental arches are in a state of equilibrium between the posture and behaviour of the lips and cheeks facially and the posture and behaviour of the tongue. This position must be such that when the mandible moves on a normal path of closure, the dentition occludes uniformly without surfaces meeting in such a way that abnormal stress is thrown on the supporting structures. If there is a malocclusion which results in abnormal stresses being thrown on to the supporting structures, then either: (*a*) The supporting structures of the teeth are traumatized; the teeth are clinically loose and are likely to be lost prematurely. This is seen all too frequently in the periodontal field of dentistry. (*b*) The abnormal contacts produce reflex modifications of the patterns of activity, so avoiding trauma.

Alveolar bone is very sensitive to pressure and only a few grams are necessary to stimulate absorption and deposition, so that the bone and teeth move to a new position of equilibrium.

As a result of these concepts, the author suggests that it is likely that a high percentage of the cases referred to as derangements of the T.M. joint are, in fact, reflex disturbances of the basic co-ordinating patterns of mandibular movement. It is the purpose of this short paper to review briefly the evidence to support this view.

It should be explained at this stage that an orthodontist sees a large number of cases with a displacing activity which do not present any symptoms, but with regard to all displacing activities, there are certain features which can be found on careful clinical analysis to support the concept (Grewcock and Ballard, 1954). They are:

(1) That the abnormal occlusal contact which produces the displacing activity can only be found when the mandible is moving slowly from the true endogenous postural position into occlusion. When the abnormal contact is made, the mandible apparently slides on it into the displaced position.

(2) In normal masticatory activity these contacts are avcided and the mandible goes into the displaced position of occlusion.

(3) If one removes, perhaps by grinding, such abnormal contacts, the individual rapidly reverts, within a matter of a few hours usually, to a normal and symmetrical closing activity.

It is suggested that the avoiding action was reflexly established and reflexly maintained by the abnormal contacts being made during idle mouth movements. It is a habit pattern of activity. Another finding is that in many of these displacing activities, the occlusal level does not bear its usual relationship to the rest position but is an overclosed position. It has been suggested (Grewcock and Ballard, 1954, 1956) that this is the result of the reflexly-disturbed patterns of activity of closure. The activity necessary to produce the displacement continues after there should have been a reflex relaxation at the normal occlusal level.

Further support comes from the electromyographic analysis of normal and abnormal cases which is being carried out by many workers. The general impression is that in normal closure there is a symmetrical and smooth activity of the masseter and temporalis muscles, these being the most readily investigated by surface electrodes, and there are also smooth patterns of action in masticatory movements.

When cases with a displacing activity are investigated, these smooth patterns of action are usually interrupted by momentary relaxations followed by peaks of increased activity. As far as is known, no work has been published on electromyographic analysis of treated cases but, as has been said already, clinically the individual reverts within a very short time to what can be regarded as normal patterns of activity when the cause of the afferent stimuli maintaining the habit patterns is removed.

Another important fact is that a high percentage of "cures" is obtained by treatment which either removes the cause of the displacement or prevents the contact of the tooth surfaces producing it. The cures are sometimes startling—a patient may have unbearable pain and yet be completely free in twenty-four hours after the insertion of a simple plate which prevents the abnormal contacts being made.

It is an interesting fact that the displacement may not be more than a 1–2 mm. shift laterally, distally or forward as viewed from the incisor teeth and yet produce extreme pain. As is now generally recognized, it is rare to find any pathology in the joint in these cases; indeed if there were it is unlikely that dramatic cures would occur so rapidly.

Many authors investigating T.M. joint dysfunction have reported finding tenderness in muscles. Schwartz (1955) said "T.M.J. pain may often be due to painful self-perpetuating spasms in muscles".

In a previous paper (Ballard, 1955), the author reviewed the biological background to complex co-ordinated muscle activity and demonstrated that it supported the view that motor activity is based on endogenously determined basic co-ordinating patterns.

In brief, there is the work of Weiss (1941, 1950), firstly on amphibia, as the result of

which he formulated the concept of myotypic responses and put forward his concept of the hierarchical organization of behaviour. Both he and Tinbergen (1951) have pointed out that in higher animals there is some evidence that this concept also applies, because they are not able to adapt themselves to nerve and tendon transplants. Further, Hess (1954) has stimulated the diencephalon of intact cats and has produced complex patterns of behaviour at the highest instinctive levels in animals. In man the results of the transposed tendons in poliomyelitis victims show that re-co-ordination is only produced after prolonged training and much conscious effort and that there are frequently temporary relapses in fatigue, indicating that the basic co-ordinating patterns are still there at their much lower level in the brain, but are being controlled at a higher level.

It is the author's contention that both the clinical evidence and the biological background suggest that a high percentage of the cases of temporomandibular joint affections are, on the physical side, either directly or indirectly the result of a reflex disturbance of the endogenous co-ordinating patterns of mandibular movement; indirectly in many cases where sudden trauma, superimposed on a disturbed pattern of activity, is the precipitating factor.

Orthodontists see a large number of cases with the reflex-displacing activity not associated with T.M.J. symptoms. Mr. Hankey has said there appears to be in many cases a psychological element. It may be that a hyperactive central nervous system becomes more readily aware of muscular imbalance but it is important not to overlook the somatic aspect of a psychosomatic disorder. Again as Mr. Hankey has said, some cases present with sudden onset. Trauma of a comparatively slight nature to an already disorganized pattern of activity might be a precipitating cause.

Clicking in the joint may be due to the lateral pterygoid taking most of the strain in such cases, with some resulting disorganization of the movement of the condyle and the inter-articular disc.

So far, disturbances of activity and not disturbances of the postural position have been discussed. Disturbances of the postural position of the mandible are well recognized. They are produced mainly as the result of the necessity to produce an anterior oral seal across an incisor tooth relationship which is not normal. An individual may posture the mandible forward in order to enable him to bring the lips together; this habitual forward posturing may be maintained for many years, perhaps for the life of the individual, in some cases. Alternatively, an individual may not only posture the mandible forward but may drop it a little in order to assist the production of an anterior oral seal by the protrusion of the tongue against the lower lip. Again this may persist as a habit pattern of activity, maintained for many years.

As far as our clinical observations go, it would appear that during masticatory activity these individuals revert to their endogenous postural position as an initial movement. There is already some electromyographic evidence to support this clinical observation. What may be important, however, is that, so far, there is no evidence to suggest that these habitual postures produce any symptoms in the musculature. Neither do they result in any disturbance in the temporomandibular joint, in spite of the fact that it is not in its normal postural position for most of the time.

The impression has been gained that undue prominence has been given in the past to variations in posture which are probably the result of inherited factors. If all the evidence here has been correctly interpreted, it would appear that pain in muscles referred to the joint might be the result of a reflex disturbance of the basic co-ordinating patterns of activity. The necessity for this reflex disturbance may, of course, be the result of inherited abnormalities, pathological conditions or trauma.

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Dr. G. O. Storey:

Before a diagnosis of temporomandibular arthrosis or dysfunction can be made it must be remembered that the joint may be affected by any form of arthritis which affects other joints.

(1) A septic arthritis may occur, usually the result of spread from local sepsis, but sometimes the result of blood-borne infection.

(2) Rheumatoid arthritis may affect the joint. It is not very common, nor is it likely to be the first joint affected, but Coates and Delicati (1931) state that after the joints of the limbs

it is the most commonly affected one, and in one series it was affected in 20% of cases. Hydrocortisone has been effective in relieving severe symptoms in a few cases.

(3) Ankylosing spondylitis may affect the joint and may produce such great limitation of jaw movement that surgical intervention is necessary to allow feeding. Other forms of infective arthritis do occur and particularly gonococcal arthritis has been said to affect the joint. However, King and others (1946) found only one case among 178 patients with arthritis due to the gonococcus or non-specific urethritis.

(4) Trauma to the joint may, of course, produce fractures, dislocations, tears of the capsule and lesions of the cartilage. The importance of minor trauma in producing chronic joint symptoms due to osteoarthritis, or in other ways, will be discussed later.

(5) Osteoarthritis does certainly affect the joint, whether the result of trauma or other factors. Bauer (1941), examining the joint pathologically in various age groups, reported cracks in the cartilage, increased density of subchondral bone and exostoses. He found these changes more commonly in edentulous elderly patients and following trauma. McLaren (1944) reported a case with cyst formation and bone degeneration following trauma. Doub and Henney (1953) have described the radiological appearance of such joints. In the early stages they describe (1) Hazing or clouding of the joint space with indistinctness of outline. (2) Slight narrowing of the joint space and retro-position of the condyle in the closed position, and (3) In the open position the condyle may be restricted in its anterior excursion, or it may have a wider excursion than normal, the result of laxity of the ligaments. The retro-position of the condyle they attribute to early absorption of the cartilage, but it might well be due to displacement of the disc forwards. It is clear that they are describing the condition of T.M. joint dysfunction, and they hold the debatable view that this condition is a type of degenerative arthritis. In the fully developed osteoarthritis there is loss of joint space, hypertrophic changes around the margins, flattening and irregularity of the joint surfaces with increased density of subchondral bone. Loose bodies may be present.

If one of these types of arthritis can be ruled out, it must not be forgotten that conditions affecting the structures near the joint may cause pain and dysfunction without involving the joint directly; any condition, neoplastic or infective of the middle ear, eustachian tube, parotid gland or other soft tissues may have this effect. Two somewhat unusual conditions were: (1) A case of scleroderma with great limitation of jaw movement due to the thickened tissue round the joint, and (2) A case of temporal arteritis where the presenting symptoms were pain and stiffness in the joint.

When all these conditions have been excluded there remains a large group of cases which do not fit readily into the foregoing categories and these have been called temporomandibular arthrosis or dysfunction. The condition is commonest among young women, and the onset often follows trauma—sometimes due to dental treatment—or there may be an abnormal bite. The main symptoms are: (1) Pain in the joint. (2) Clicking or snapping. (3) Limitation of movement. These may be present separately or together. Often episodes of clicking, pain or limitation pass off spontaneously. Clicking, particularly, which is regarded as being due to the slipping of the condyle over the posterior edge of the disc is fairly common among people who have never sought advice and some can produce it at will. Pain and limitation may appear only after a lag of several months. Whether those affected more severely eventually have spontaneous relief is less certain. I will quote one case which shows the importance of a long follow-up. A man aged 50, ten years ago had a dental extraction of the third right mandibular molar under subregional anæsthesia. There was no undue trauma, but two days later he could hardly open his mouth, although there was no pain. Manipulation produced immediate relief, but two hours afterwards the condition was as bad as before. No further treatment was given and gradually over a period of two years the condition improved and there have been no symptoms since, after ten years. Whether this is the usual outcome cannot be said, but it is important to know, because if spontaneous recovery is the rule it weighs against the theory that this condition represents an early stage of degenerative arthritis initiated by minor trauma, since in this case one would expect it to have run a progressive course. Further as Hankey (1954) has shown the condition is commonest in young people and not in the osteoarthritic age group. Good X-ray evidence of osteoarthritis is usually lacking although retro-position of the condyle is often seen. Further MacGregor (1955) found that chronic pain was rare in a follow-up of patients after fracture dislocation of the joint—although his was a small series.

Pain.—Pain may not be confined to the joint itself. Costen (1934) and later writers have described various other symptoms which may be associated, these include various neuralgic pains radiating over a wide area even to the neck, tinnitus and deafness. Goodfriend (1947), in fact, attributes many cases of deafness to disturbance of the T.M. joint.

Costen (1934) originally believed that these symptoms were produced by direct pressure of the displaced condyle on the nerves which lie close to the joint and on the eustachian tube and tympanic plate. This view has been generally rejected, particularly by Sarnat

(1951), indeed it would seem that severe degenerative change would have to be present before direct pressure could occur. It seems now to be accepted that these symptoms when they occur are the result of pain referred via the branches of the auriculo-temporal branch of the V nerve which supplies the joint and thence to the other branches of the V nerve. Ear symptoms have been attributed to spasm of the tensor tympani muscle. The wider spread of the pain outside the area supplied by the V nerve is harder to explain, but the fact that the nucleus of the V nerve descends into the cervical cord has been adduced to explain the pain in the neck.

Referred pain may also be caused in another way. Namely, that pain or stimuli from distant structures may be referred via these same nerves to the joint and the muscles operating the joint, thus producing pain and dysfunction of the joint. The importance of referred pain is illustrated by the case of a man aged 74 who had typical trigeminal neuralgia affecting the third division of the V nerve with a trigger point in the lower lip, he also had pain and dysfunction of the temporomandibular joint. A block of the inferior dental nerve was carried out which relieved both his neuralgia and also his temporomandibular symptoms. Relief lasted six months and then symptoms recurred. Extraction of a tooth in the lower jaw then produced relief.

Infected sinuses may also produce this referred pain. It seems then that pain, and with it dysfunction of the T.M. joint, can be part of the syndrome of facial pain, and Stones (1956) has recently reviewed this subject. The ætiological factors are too numerous to be mentioned here, except to say that cervical spondylosis has been mentioned by Campbell and Lloyd (1954) and Wyburn-Mason (1953) as a cause of facial pain, the ramifications of the auricular nerve being the nerve involved and the sympathetic system has been incriminated by Campbell and Lloyd (1954) and Fay (1932).

It has been said that aching pains in muscles and bones are carried mainly in afferent sympathetic fibres. On the motor side of these reflex mechanisms, it is clear that a study of the actions of the muscles operating the joint is of great importance and electromyography can contribute in this field. The published papers by Prudanskys (1952), MacDougall and Andrews (1953), Tulley (1953) and Greenfield and Wyke (1955) deal mainly with the patterns of normal activity, but the work of Moyers (1949) has suggested that sometimes there may be an overaction of the posterior fibres of the temporalis muscles which would have the effect of drawing the condyle posteriorly as is seen in this condition. However, much more work is necessary in this field before a definite conclusion can be drawn. The few cases that I have investigated have not shown any gross abnormalities.

Treatment.—Apart from the dental aspects of treatment many other methods have been tried with success. This perhaps emphasizes the psychological aspects of this problem, and as Craddock (1944) has said, the more dramatic the response to treatment and the newer the method employed the less are organic factors likely to be present. Various substances have been injected into the joint. Sclerosing substances to correct the laxity of the ligaments, Novocain and hyaluronidase have all been tried with some success, and more recently hydrocortisone. Doub and Henney (1953) have claimed a high proportion of cures in their cases. In a small series I have treated with intra-articular hydrocortisone, about half seem to respond well. The ones that did best seem to be those with clicking joints which had become stiff and painful. Hydrocortisone relieved the pain and stiffness although the clicking usually persisted.

Surgical measures may be undertaken usually when conservative methods have failed. Meniscectomy and condylectomy have been used.

To summarize the factors which have been regarded as important in the causation of this condition:

(1) Trauma, the result of abnormal bite or other cause.
(2) Reflex factor producing pain in the joint and neuromuscular imbalance or spasm.
(3) Psychological factors.

Now these factors are also those which are said to be important in the causation of another condition, namely the stiff shoulder, although it would be unwise to draw too close an analogy between the two. Nevertheless, in view of this and also because of the possible importance of the sympathetic system in the causation of facial pain, it seemed worth while to try the effect of stellate ganglion block in temporomandibular dysfunction since this is sometimes effective in the stiff shoulder. The temporomandibular joint receives its sympathetic fibres from this ganglion also. Only one patient has been treated in this way so far. It is worth quoting this case because it shows other aspects of this condition. This patient, a woman of 49 years of age, for a year had a clicking right T.M. joint and had recently been having pain in the joint on chewing; she also had pain and soreness around the ear. For many years she also had pain and stiffness in the neck, although no limitation of neck movement. There appeared to be psychological factors present, and she was unhappy at her work. Examination showed facial asymmetry suggesting the possibility of an abnormal bite although

this has not been assessed. There was clicking and tenderness of the joint. X-ray examination showed retro-position of the condyle on the affected side. Hydrocortisone was first tried and 1 c.c. was injected; this produced soreness for two days, and then relief of symptoms for one week, although clicking continued. Symptoms then recurred. A second and third injection were much less effective. A stellate ganglion block was then performed and immediately after there was relief of symptoms, and she was able to eat an apple painlessly. Relief has so far lasted fourteen days although clicking is still present. This case illustrates some of the complex factors which may be present, and it would be unwise to overemphasize the effect of the stellate ganglion block in a single case.

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DISCUSSION ON AN EVALUATION OF THE METHODS OF INCREASING MUSCLE STRENGTH

Dr. H. D. Darcus (External Staff, Medical Research Council, Nuffield Orthopædic Centre):

Since the beginning of the century, very little new has been found out about the function of muscles in the intact human body or the ways of improving it, probably because analogous conditions cannot be reproduced in other animals, which have been the "subjects" in the majority of the studies of muscular activity. One of the few well-established facts is that the performance of muscles can be improved by systematic voluntary exercise, although no agreement has been reached regarding the most effective way in which this can be achieved or the underlying structural and functional changes that occur. No doubt because of this, there is no generally accepted method of muscle training, but the number of routines that have been described, and the range of instruments that have been devised, bear witness to the extent of the determination of the workers in this field. Sooner or later the scientific basis of our methods must be examined, if only to avoid the possible retarding influences of general impressions and theoretical approaches.

In discussing the subject of muscle training, we should define the various expressions of muscular contraction and the part each plays in the functional activity of the locomotor system; indicate the functional and morphological changes that occur in the exercised muscles and in the nervous system; decide the immediate objectives of exercise and review the types of exercise that can be used and the ways in which they can be carried out.

Expressions of muscular activity.—The characteristic property of skeletal muscle when stimulated by nervous impulses is that of contraction with the production of mechanical energy. The tension derived from this mechanical energy will manifest itself in various ways depending on, for example, the external conditions, the local state of the muscle and the activity of the nervous system.

The activity of muscle may be expressed as strength, endurance, speed and co-ordination of movement. Although divided in this way for the purposes of discussion, it is evident that each is related to the other to a varying extent under normal functional conditions.

The strength of a muscle has assumed various meanings but here we shall define it as the maximum applied tension that can be developed, instantaneously on a single occasion, to overcome or attempt to overcome an imposed load or resistance. It will depend on the potential tension of the particular muscle at "the disposal of the nervous system", and

the greatest proportion of this that can be called into action at any one time, which is essentially the definition proposed by Hansen and Lindhard (1923). It will also be influenced by the degree and co-ordination of activity of other muscles in functional relationship with it, that is, the synergists, antagonists and fixators.

Endurance is a function of the capacity of a muscle to maintain or repeatedly develop a certain degree of tension. This can either be a fixed proportion of the maximum strength of any particular muscle group or a standard level irrespective of this maximum. Failure to distinguish between these two criteria may cause confusion in considering other factors affecting endurance. For instance, a strong person may be able to maintain the same level of tension for a longer period than a weaker one, but be unable to maintain for as long the same proportion of their maximum strength. This is indicated by the results of Tuttle *et al.* (1950) on the relation of maximum grip strength to grip endurance.

The speed is related to the rate of increase in tension, the resistance to be overcome, the number of times the muscle has to contract and the range through which its contraction moves a joint. In general, the greater the length of a muscle and the lighter the load, the faster it can shorten. As the speed is not constant but rising to a peak and then falling off, one should probably record it in terms of the maximum attainable.

Co-ordination is the ability of muscles to act with each other in the correct sequence, at the proper speed and with the appropriate tension.

Although these qualities are related, the possibility that the restoration of normal function demands exercises in which all are equally involved or in which one or other predominates should be considered before embarking on any training routine. For instance, a method may improve one aspect of muscular activity but at the same time adversely affect another. It is possible, for example, that certain strength-promoting techniques may reduce speed of movement. It has been recommended that different methods should be used to produce the desired result. For example, it is said that an increase in strength is favoured by heavy resistance exercise, endurance by rapidly repeated contractions and co-ordination by light muscular work (Elkins and Wakim, 1947; Delorme and Watkins, 1948; Asmussen, 1949; Wakim, 1950; Lundervold, 1952; Knapp, 1953). It is also stated that different types of exercise induce different changes in the muscle. For instance, exercises of strength are said to cause hypertrophy and those of endurance an increase in the capillary bed (Wakim, 1950).

Changes in response to exercise.—However, before we can design and prescribe exercise, or any other treatment, to improve muscle function on a more rational basis, we should attempt to determine the underlying changes that occur in the neuro-muscular system in response to exercise; changes which are, as yet, not fully understood. Modifications in structure and function may occur at various levels; which, for the present purpose, will be divided into those occurring in the muscle, increasing the potential tension available, and those in the nervous system, allowing the best use to be made of this potential. Various aspects of these effects of exercise have been reviewed by Steinhaus (1933).

Muscle changes: The size of normal muscles can be increased as the result of repeated exercise. This has been reported in animals (Morpurgo, 1897; Siebert, 1928) and in man (Hellebrandt *et al.*, 1947; Delorme *et al.*, 1952; McMorris and Elkins, 1954). This is not due to an increase in the number of the constituent fibres (Siebert, 1928) but to an increase in the diameter of the individual fibres (Morpurgo, 1897; Schneider and Karpovich, 1948). This is interpreted as indicating that each contains a larger amount of sarcoplasm (Elkins and Wakim, 1947) although it might equally well be accounted for by shortening of the fibres without any change in volume. Even if there is an increase in the volume of a muscle, it does not necessarily imply that the muscle tissue is wholly or even partly responsible. It may be caused, or at least contributed to, by additional connective tissue (Wakim, 1950; Anderson, 1951) or blood vessels (Petren *et al.*, 1936). Temporary swelling that occurs immediately following activity (Hough, 1902; Starkweather, 1913) may be ascribed to an increased amount of intramuscular fluid resulting from an accumulation of the metabolites of the chemical processes accompanying contraction. Indirect evidence for this is provided by the fact that the volume returns to normal within a few hours (Hough, 1902).

Assuming that hypertrophy of normal muscle fibres does take place, the processes concerned may not be the same as those involved in the regaining of normal size of fibres which have atrophied as the result of disuse or denervation. Presumably, there must be some factor or factors which control the ultimate size. These might include mechanical conditions, such as limitation of space for expansion, or nutritional demands, which may be related to the adequacy of the blood supply. Thus, for example, degeneration of some of the muscle fibres might give more space to those remaining to hypertrophy providing they receive sufficient nourishment.

Though the size of muscle fibres may be increased by appropriate exercises, we still do not know how much this contributes to improvement in muscle strength. It is commonly

stated that the larger the diameter, the greater the tension that a muscle fibre can develop. However, in an intact muscle, this relationship is difficult to determine. Various attempts have been made to express it in terms of the maximum tension per square centimetre of the physiological cross-sectional area—that is the area when every fibre is transected at right angles to its own long axis—which is a function of the diameter of the fibres and their number. This has led to widely divergent results, owing to the difficulties that have to be overcome and the assumptions that have to be made. The maximum tension has been measured with the joint on which the muscle is acting, in different positions—so that the length of the muscle varies as does its leverage. It is assumed that the result obtained is the sum of the activity of all muscle fibres—a state of affairs that never exists normally. Furthermore, the difficulties of calculating the physiological cross-sectional area with any accuracy, in muscles in which fibres are running in various directions, and of estimating the area to allow for non-muscular tissue, are immense.

It seems fair to conclude from these considerations that muscle bulk is not a reliable criterion of strength. In fact it has been stated that exercised muscles can increase in size but not in strength and vice versa (MacQueen, 1954).

Apart from possible changes in use, there may be variations in the intimate structure of the muscle fibre, which may or may not affect its function. It is also conceivable that the arrangement of the muscle fibres within the muscle may alter, becoming re-aligned so that the pull of each is less oblique, resulting perhaps in an increased applied tension during contraction.

It has also been suggested from the results of animal experiments, that repeated exercise produces certain biochemical changes in the muscle fibres (Palladin, 1945), such as an increase in myoglobin (Whipple, 1926; Lawrie, 1953) and glycogen content (Embden and Habs, 1926). Such modifications might provide the basis of a better store of fuel and oxygen to be drawn on, particularly during a sustained contraction, and in that way improve endurance.

An increase in the intramuscular capillary network is reported as occurring in animals (Vanotti and Magiday, 1934; Petren *et al.*, 1936), which provides the exercised muscle with an improved supply of raw material and a better disposal of waste products. The formation of new capillaries, opening-up of hitherto unused capillaries and a better use of the available channels have been considered important adaptive reactions in trained human muscles (Maison and Broeker, 1941; Jokl, 1948). Although this seems to be a reasonable supposition, there appears to be no direct evidence of it in man.

The fibrous tissue framework of the muscle may also undergo changes. If a muscle is continuously worked under conditions conducive to the formation of intramuscular œdema, deposition of further fibrous tissue may occur, which might interfere with the contraction of the muscle fibres (Anderson, 1951). An increase in fibrous tissue is said to be found particularly in those muscles subjected to exercise of a "heavy nature" (Wakim, 1950).

Neuro-muscular adaptations: Apart from the structural and biochemical changes, there are probably much more important neuro-muscular adaptations, which result in the elimination of unnecessary muscular activity and an increased use of the muscular tissue of direct value to the task (Lundervold, 1951).

During the initial phase of any training procedure, improvement may be partly accounted for by the acquisition of skill. The patient learns how to perform the prescribed task, contracting the proper muscles in the correct sequence and at the same time reducing non-productive activity so that more of the available effort can be directed to the "job in hand".

As a result of training, there is also probably, with the same voluntary effort, an increase in the number of muscle fibres contracting, with a correspondingly greater output. How this is achieved is still a matter for speculation, although as early as 1907 Hellsten concluded that improvement in muscle strength following exercise was due to an increase in "the intensity of muscle innervation".

The increased activity may be explained by the increased use of those muscle fibres normally involved and by the recruitment of others. If this is so, a greater number of effective nerve impulses must excite more muscle fibres than previously. This could be explained on the basis that the anterior horn cells themselves receive more impulses, the resistance to their passage across the synapse and the neuro-muscular junction is reduced and that a greater number of anterior horn cells are stimulated.

If training is accompanied by an increase in the number of active motor units, what were the extra units doing before? It is hard to believe that some motor neurones and their associated muscle fibres were lying dormant and being held in store in case of need, as has been suggested (Gould and Dye, 1932; Kabat and Knott, 1953). A more satisfactory explanation seems to be provided by the work of Seyffarth (1941) and Denny-Brown (1949). They have shown that motor units become active in a definite sequence and, in muscles that have more than one function, the sequence of recruitment varies with the different

movements produced. For example, in biceps brachii, there are separate groups of motor units initiating flexion, supination and combined supination and flexion, but as the contraction increases, motor units involved primarily in one movement are used in the others. For instance, during flexion, certain motor units only appear at a very high tension, whereas the same units go into action on the slightest degree of tension during supination. The spread of motor unit activity may be explained on the assumption that at the beginning of contraction, one limited field of neurones is excited and as contraction increases this field widens concentrically. If a muscle is capable of producing more than one movement, there may be a separate centre of neuronal activity for each one but with the related fields of neurones overlapping. Thus, as the contraction is developed, activity spreads farther from the initial focus into neighbouring fields with the excitation of neurons primarily concerned in other movements by the same muscle and of those of associated muscles. Sharrard (1955) has demonstrated the overlapping pattern of neurons in the anterior horns innervating functionally related muscles which provide the anatomical basis for such a concept. As the result of training, one may suggest that the "irradiation" occurs more readily and is more extensive.

Changes bringing about the increase in intensity and spread of motor unit activity may occur at different levels of the nervous system receiving impulses from widely different sources. There can be no doubt that afferent information from the muscles, and possibly other peripheral sources, is of importance in the control of muscular contraction. It is well known experimentally that damage to the posterior roots adversely affects muscular activity (Mott and Sherrington, 1895; Hyde and Gellhorn, 1949; Lassek, 1953). It is possible that stimuli originating in the periphery are of even greater importance in training. As far as the muscles themselves are concerned, it has been shown that their mechanical response is increased by the tension they develop and the degree to which they are stretched, this being attributed to reflex proprioceptive "drive" or "facilitation" (Beritoff, 1924; Gellhorn, 1953). If such reflex stimulation does occur, the receptors which are responsible should be defined. Although the neuro-muscular spindles have a low threshold and when stimulated do cause reflex contraction of associated muscle fibres, they adapt very rapidly and are only affected by stretch (Matthews, 1933; Kuffler *et al.*, 1951). It, therefore, would seem unlikely that they would assist in a sustained contraction of a muscle remaining at the same length or shortening. However, Merton (1953) has proposed that when a muscle contracts the intrafusal fibres of the neuro-muscular spindles shorten at the same rate as the main muscle. As the spindle is probably stimulated by the relative difference between its length and that of the main muscle fibres lying in parallel with it, a spindle discharge may thus be maintained. It has also been submitted (Granit *et al.*, 1955) that impulses from the higher centres, as well as passing to the larger anterior horn cells and being relayed from there to the muscle causing a contraction, also travel to the smaller anterior horn cells producing instead a contraction of the intrafusal fibres of the neuro-muscular spindles, which, although giving rise to a negligible tension, is sufficient to activate the associated afferent receptors and to elicit through the stretch reflex arc a contraction of the main part of the muscle. Thus one can picture the self-stimulating system of muscle being augmented by supraspinal impulses raising the level of excitation of the anterior horn cell either directly, or indirectly, through stimulation of the receptors.

The number of these descending impulses will depend on the motivation and concentration of the patient. However, the general level of excitation of the higher centres may be increased by impulses originating in the active muscles (Gellhorn, 1953), which is in accord with the concept that sensation and movement form a single continuous process and that the activity of the motor cortex depends on information received from the receptors (Walshe, 1947; Gooddy, 1949). Bates (1951) has, in fact, recorded potential changes in the region of the motor cortex during muscular contraction which has been interpreted as representing the arrival of afferent impulses from the periphery, and Dawson (1947) has found changes in the EEG on stimulating a peripheral nerve in man, which has been considered due to the proprioceptive impulses evoked. Thus, it seems fair to assume that muscle activity also reinforces itself by its stimulating effect on the motor cortex and probably other motor centres of the brain. It is possible that the effect is not confined to the same muscles but is distributed over a wider area. For instance, cortical "facilitation" may explain the increase in amplitude of the knee-jerk when the hands are clenched at the same time (Bowditch and Warren, 1890).

Besides an increased number of impulses passing along the descending pathways, repeated contractions may result in other pathways being "opened up" so that there are more available channels along which impulses can travel to the anterior horn cells innervating the active muscles. Such a formation of collateral routes would be of importance in cases in which the usual ones have been interrupted.

Thus one can envisage that muscular contraction once initiated sets up a circle of events

which may be traced from an increased frequency of stimulation of a greater number of proprioceptive receptors, to the impulses which arise stimulating more intensely a larger number of anterior horn cells, either directly or indirectly through their effect on the higher centres, to an increased rate of contraction of muscle fibres in more motor units.

The repetitive barrage of impulses circulating around the neuro-muscular system, besides facilitating synaptic and neuro-muscular transmission, may also, if repeated often enough, reduce resistance to the relay of the impulses at these junctions, thus allowing more to pass from one link in the neuro-muscular chain to the next. This is indirectly supported by the fact that repeated electrical stimulation of the proximal end of a posterior root results in an increased reflex muscular contraction (Eccles and McIntyre, 1953). The final result may depend to some extent on the anatomical nature of the various synapses, that is, the differences in the intimacy of contact of one neurone with another, their excitability and the number involved. For instance, one would expect the stretch reflex to be readily affected because there are only two neurones in the arc, which are in close synaptic contact, and the anterior horn cell has a high level of excitability; whereas reflex arcs including internuncial neurones would be less susceptible.

So far we have only considered the positive nervous mechanisms involved in muscular contraction but the possible "interfering" role of inhibitory influences of the nervous system cannot be overlooked because inhibition is just as much a part of its function as excitation. Therefore an improvement in muscle function, brought about by training, may also be due to a reduction in inhibitory impulses, originating in the periphery or passing down from higher centres, impinging on the anterior horn cells. Apart from the more conscious inhibitions, such as the unwillingness to contract a muscle because of pain or the fear of producing it, contraction may be restrained by impulses arising from the neuro-tendinous spindles (Granit, 1950). These endings are sensitive to tension whether induced passively by stretch or actively by the contraction of the muscle, but they have a high threshold and may form part of a protective reflex mechanism preventing excessive stretching or contraction of the muscle, rather than entering into the control of muscular activity which is within normal limits. However, there is evidence that autogenous reflex inhibition may occur. It has been shown, for example, that beyond a certain level of tension the more or less regular increase in the frequency of discharge of active motor units and the recruitment of those previously inactive is replaced by a more irregular and intermittent pattern marked by the appearance of larger slowly discharging motor units and by the previously rhythmically contracting motor units tending to discharge in bursts separated by periods of inactivity (Norris and Gasteiger, 1955). It is postulated that this radical change with stronger effort is caused by the activity of the larger motor units exerting in some way an inhibitory influence at an undetermined level of the central nervous system. There is also accumulating evidence of the existence and importance of the inhibitory part of the extra-pyramidal system (Magoun, 1950). However, the functional organization of this system and its precise relationship to muscular activity is largely unknown. In spite of this, it is tempting to suggest that part of the neuro-muscular adaptations that occur as the result of training is a reduction in its effect on the anterior horn cells during contraction.

Having outlined some of the changes in the neuro-muscular system that occur as a response to exercise and their possible basis, one must conclude that the changes that occur in the nervous system are of prime importance and that those in the muscles are secondary to these. Furthermore, although the neural components being numerous and inter-connected in a complex manner render them more prone to interference, it does on the other hand provide a basis for plasticity so that, if appropriately stimulated, compensation can be made for any permanent breaks in the nervous network by developing alternative routes. Training can be visualized as a method of increasing the use of the normal path-ways and producing new ones.

The purpose of therapeutic exercise.—The main uses of exercise are to restore or improve muscle function so that the patient can carry out his ordinary tasks, by maintaining the activity of the unaffected muscles, increasing that of those affected and, if necessary, the recruitment of other muscles to assist or take over the function of those affected. The object is to ensure as far as possible the recovery of function rather than to restore normal morphology. It may be preferable, for instance, to re-establish muscle balance even though the strength of some of the muscles concerned is below normal or to encourage compensatory or "trick" movements when the prime movers cannot carry out their work effectively.

It is probable that, in general, these aims can be best achieved by prescribing exercises that are designed to produce maximum activity of the involved muscles and to maintain or restore their blood supply rather than to concentrate on the development of muscle bulk or strength.

The types and techniques of exercise.—Even if one is satisfied with these aims, the general

principles of the type of exercise required to bring them about are not fully known. There are many variables that should be considered. Amongst these are the extent and pattern of the muscular activity that is imposed. Should the object be to concentrate on isolated muscle groups, small groups of muscles involved in simple movements, or on mass movements? Should the pattern resemble that occurring normally or can the affected muscles be exercised in another way? Apart from the advantage of practising what one wishes to acquire, a normal pattern is easier to learn than those requiring new or even unnatural associations or sequence of the contractions. Furthermore, if the latter are carried out, ultimate functional recovery may be delayed by inhibiting the normal habit (Griffiths, 1943), although natural co-ordination can eventually be re-established (Bair, 1903; Weiss and Brown, 1941; Buchthal, 1949). Another question is whether or not the exercise routine should attempt to retrace the development of the movement it is wished to regain. As the result of injury or disease, the most recently acquired movements are often the soonest lost and the last to return (Jackson, 1931–2). An example of this is the "reversion" from the "ball" grip, which involves opposition of the thumb, to the cylinder grip following substantial injury to the hand or forearm (Griffiths, 1943). In such a case, would recovery be more rapid if initially the exercises were directed at improving the cylinder grip before attempting to restore the ball grip by active participation of the thumb? Other examples have been given by Hansson (1950).

Another variable is whether the contraction should be isometric or isotonic. Isometric contractions are not often favoured possibly because they are found boring (Ionesco, 1949) or because improvement is not immediately obvious (Asmussen, 1949). On the other hand, they have been recommended in the treatment of partially paralysed muscles to minimize the friction that might occur between active and inactive parts and the possibility of this causing further damage to the muscle (Lundervold and Seyffarth, 1942). They may also have a place when movement is contra-indicated, for example, because of pain or following joint operations. There is no clear evidence as to which form of contraction is associated with the highest degree of muscle activity or which gives the greater speed or degree of recovery. Eccles (1944) on the basis of animal experiments concludes that, from the practical aspect of treatment, disuse atrophy is best counteracted by allowing muscles to shorten during their contraction and that strong voluntary contractions without movement are reasonably effective in maintaining the condition of the muscle. Darcus and Salter (1955) found no significant difference in their effect on the increase in strength of normal muscles. A comparative study on weakened muscles does not appear to have been made. If isometric contractions are used, they can be effected by the muscles either attempting to shorten as in trying to compress a heavy spring or by resisting lengthening as in holding a weight. Whether or not the mechanical response of the muscles is the same under the two conditions is not known.

Another factor is the position of the joint in which the muscle group should be exercised. It is well known that the contractile force increases as the muscle is stretched to the maximum length that it can attain in the body (Ralston *et al.*, 1947), and it has been shown in the monkey that, in this state, the muscular activity resulting from cortical stimulation is greatest (Gellhorn, 1949, 1953) but, in this position, the applied force that can be developed is often small because of the mechanical disadvantage (Darcus, 1954). Should one, therefore, exercise the muscles in the joint position which favours the production of the greatest muscular activity, or the one in which the applied force is maximum, should they not coincide? The latter has the probable advantage of being the one that is instinctively adopted when maximum exertion is required and in weakened muscles perhaps the only position in which the patient can see anything for his efforts, although it seems to go counter to the idea that the stretched position is desirable because of the increased reflex stimulation. If isotonic contractions are used, the variables include the range of movement required and, if this is less than the total, the part of it to be passed through.

Whichever type of contraction is decided upon, other factors to be considered are whether the contraction should be the maximum possible or some proportion of it, the rate at which it is developed, the duration of each, the rate of repetition, the length of the exercise period and their number and placement during the day. Most routines are based on an ergographic technique in which the subject is required to repeat submaximal isotonic contractions in rapid succession. Initially, in such a procedure, the muscular activity is below the maximum that can be voluntarily induced, but as the exercise is continued more and more of the muscle is contracted in order to maintain the work output (Knowlton *et al.*, 1951; Lundervold, 1951). If, as has been suggested, maximum activity is required, this seems a time-consuming way of producing it. However, even when a maximum contraction is the primary aim, it is probably not achieved either because the patient does not know how to make a maximum effort, because of fear of causing pain or damage to an injured limb, or because of the unwillingness of the patient to endure the discomfort that

a maximum exertion may cause, and there appears to be no simple way in which one can check on the level reached.

The general plan of treatment will also depend on whether or not "fatigue" should be allowed. Many views have been expressed on this problem from those who believe that fatigue should be avoided at all costs to those who consider its production to be an essential part of the exercise. The issue is further clouded by what precisely is meant by "fatigue". Whatever may be the correct answer, it is reasonable to suppose that the "dosage" of the exercise prescribed should not be subjectively unpleasant or produce residual effects such as muscle stiffness or soreness, which might deter the patient from carrying out the exercise on a subsequent occasion.

The techniques for providing and measuring the effects of exercise are numerous. Apart from gravity and manual resistance, there are many devices, usually incorporating springs and weights, to produce the load against which the muscles have to work (Salter, 1955). The optimum routine and apparatus will depend on what the muscles are expected to achieve and how they are expected to do this. We can only evaluate methods when we use criteria that will allow us to judge the effects of different methods on the various aspects of muscle function.

Evaluation.—In the evaluation, we can either measure the external effects of muscular contraction or the changes which have been produced in the structure and function of the muscles. Of the external effects, we may assess the general or local functional state by testing the ability to carry out a normal task, such as walking or hand grip, or measure the various component expressions of muscular activity, such as strength, endurance, speed of movement and co-ordination. Of the changes that may occur in the exercised muscles, we might attempt to measure muscle bulk and to determine the cause of any alterations, the degree of muscular activity and the blood supply of the muscle. In many of these measurements, there may be considerable incidental variations in any one subject on different occasions, apart from those produced by the exercise, for which various explanations have been put forward (Lombard, 1892; Fischer, 1947; Weinland, 1947). Some idea of the magnitude of these variations may be gained from the finding of Bechtol (1954) that hand-grip strength of any individual may fluctuate up to 30% during a day and about 10% from day to day. The necessity for rigid control of environmental, physiological and psychological factors in this type of investigation has been emphasized by Taylor and Brozek (1944), but, however careful one is, unanticipated variables may creep in which may account for any of the changes observed.

If we can obtain reliable data on the effect of training, with what can we compare them in order to gain some idea of its extent? As, under clinical conditions there will probably be no "normal baseline" measurements, we might compare measurements taken before and after the exercise of the same muscle group or of the corresponding group on the opposite side of the body, if we can assume this to be normal and unaffected by the exercise. A comparison with information collected from other sources is difficult, because of the differences in the methods used and obvious individual variations.

Conclusions.—It appears from a review of the work that has been carried out on muscle re-education, and in allied fields, that it is still only possible to hypothesize as to the optimum method of improving muscle function and it seems that perhaps too much emphasis has been placed on muscle strength and not enough on other aspects of muscle activity or muscle function as a whole. There are still many unsolved problems. For instance, we need to find out more precisely the changes that occur in the neuro-muscular system with exercise, by what methods these can be brought about and their relationship to functional recovery. It seems necessary that an integrated attack should be made on these problems with the aim of formulating the best methods of restoring muscle function.

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Dr. D. A. Brewerton: The problem of increasing muscle strength will be considered here under four headings: crude strength; strength with a painful joint; strength during function; and motivation. Each division has its own problems and principles.

Crude strength.—The simplest method of measuring muscle strength is to get the subject

to put his muscle against a calibrated spring balance—or to lift a heavy weight. It is not surprising, therefore, that we know most about this type of strength and its development.

To develop this "crude strength", we use exercises against very strong resistance. The patient has a period of warming-up first. Then he contracts his muscle against the greatest resistance that can be overcome ten to thirty times at a session. This procedure is repeated three to five times a week. Careful record is kept of the resistance used and this is increased according to the progress made.

Dr. Darcus has discussed some problems related to such methods. I shall mention only one which we have studied—and that with a negative result. We wanted to know whether it mattered where in the joint range the maximum resistance was applied.

First we developed an apparatus for measuring the strength of the quadriceps in different positions of the knee-joint. This showed that the force with which the knee can be extended is two or three times as great when the knee is bent to a right angle as when it is nearly fully extended. By contrast, when a patient does exercises by lifting a weight attached to his foot, the resistance reaches a peak as full extension is approached. This means that the load is greatest at the point where the extensor apparatus is least efficient. In fact, in such exercises, the muscle is required to do no serious work except in the last 20 degrees of extension. Is this right? What if the patient needs greater strength when the knee is bent—for climbing stairs or getting out of a chair? To answer this problem, we developed an apparatus by which resistance could be applied at any point in the range, or proportionate to the patient's ability throughout the range. Armed with this apparatus, we measured the force of extension in different positions in 100 normal and 400 abnormal conditions. We also treated 80 patients on this apparatus, making weekly sets of measurements of their strength in 5 different positions.

As a result we reached two conclusions: the first that when the quadriceps is weak in one position it is proportionately weak throughout the range—unless pain inhibits contraction in a particular position, or there is "lag" after a patellectomy; the second conclusion was that when giving resistance exercises the position at which the maximum resistance is applied is *not* important unless the joint is painful. I feel that this is an essential basic principle which must be established or disproved by further work. We may, however, question two common practices. One is to give exercises with maximum resistance in the extended position even when this is the most painful part of the joint range. The other is to insist on a similar type of exercise when the patient is too weak to straighten the leg against the force of gravity. This involves a cumbersome method of laying the patient on his side with the leg suspended by slings—a most unnatural attitude. Surely under either of these circumstances it is better to choose a different range in which to apply the resistance.

The simplest answer to our problem, then, is that "crude strength" is developed by strong, resisted exercises; these may be static or dynamic; and the maximum resistance may be applied in any position.

Unfortunately there are many exceptions to these basic principles and they can seldom be applied without some modification.

Strength with a painful joint.—The presence of a painful joint has a profound effect on the problem. This is a distinction which deserves emphasis.

We now introduce the most important principle: that the joint condition should not be made worse. This affects all three principles outlined for developing "crude strength".

Firstly, it is unwise to apply maximum resistance. The resistance must be less; and this poses a new problem best illustrated by an example. A man with a weak quadriceps and a normal knee may be given a 20 lb. weight to lift twenty times each day. If the knee then becomes painful he may be able to lift only 10 lb. because pain inhibits muscle contraction. But the muscle itself is not changed and as far as it is concerned 10 lb. is a small weight. Should then this smaller weight be lifted more often—50–100 times a day—or better still 10 times every hour throughout the day? Probably this is so but we need more evidence to prove it.

Secondly, if the joint is very painful, there is no question about it—the exercises must be static and not dynamic. Even when the joint is less painful static exercises are usually preferred.

Lastly, the position in which the resistance is applied *is* important. The amount of pain varies in different positions and is usually most at the extremes of joint range. Such pain strongly inhibits voluntary contractions; consequently the maximum resistance is best applied in the least painful position—usually in the middle range. Of course, the position may also be determined by other medical or surgical considerations.

This last principle is best illustrated by an exaggeration of the problem. If the last few degrees of extension of a rheumatoid knee are obtained only with pain and difficulty, quadriceps contraction in this position will be weak. One can either say: "the muscle is

weak in this position; we will exercise it in this position and thereby restore full active extension"; or one can say "the problem here is principally in the joint which we will treat. We will also strengthen the muscle in the middle range where voluntary contraction is not inhibited by pain". I think that the latter view is correct.

Strength during function.—So far we have considered the sort of strength that can be measured by a dynamometer under experimental conditions. Often, however, we are much more interested in the performance of activities requiring strength than in strength as an isolated phenomenon. Admittedly this brings in many other factors such as co-ordination, or speed of reaction but, in fact, these functions cannot be separated.

Consider the subtle blends of strength and other muscle functions involved in athletic training. Most international runners now do some weight training—meaning the rhythmical use of relatively light weights—but weight-lifting and heavy resistance work is usually discouraged in the belief that it may "slow down the reflexes". Shot putters combine weight lifting, strong functional activity, and speed of action as provided by sprinting. Weight lifters do some highly specialized weight work but also add a lot of general functional exercises. All would agree, however, that the most important parts of the training are running for the runners; shot putting for shot putters; and weight lifting for the weight lifters. In other words it all depends what you want your muscles for.

This serves to introduce yet another set of problems and basic principles.

Firstly we have muscle education and re-education. In poliomyelitis during the early recovery period it is common for a muscle to be dropped from the normal pattern of functional activity because it is weak. This neglect may persist into the late stages despite good recovery of the muscle. Continuing to walk with a straight knee because the quadriceps *used* to be weak is a good example. Full restoration of strength in such muscles is primarily a matter of re-education so that they are used again in everyday activities. It is not enough that a muscle should be able to contract on the physiotherapy plinth. Its use in walking, running and working should become automatic—and it is one of the major aims of remedial exercises and occupational therapy to see that this is achieved. How many of us have heard a patient say "But, Doctor, I only do it that way during my exercises"?

Secondly, we must have strong, dynamic exercises of functional significance. This means realistic gym work and occupational therapy. Because a complicated learning process is involved these exercises must be done repeatedly—not just a small number of times as for crude strength.

Lastly, on some occasions the exercises must be specific. The man learning to put the shot became good at putting the shot and not necessarily at throwing the discus or the javelin. In the same way, if weakness causes difficulty when climbing stairs or getting out of a wheelchair one of the best answers is repeated practice in climbing stairs and getting out of wheelchairs. This introduces "skill". Unfortunately its physiological basis is obscure, but it is still an essential part of full function which we must use at every opportunity.

Motivation.—We are all familiar with the major psychological obstacles that prevent patients from doing their exercises effectively: the man suing for compensation; the man who fears that his fracture site will give way; and the old lady who would rather stay in bed—but what about the "normal" man who has no such obvious problems. With a prolonged illness it is inevitable that everyone undergoes days of depression and defeatism; when he thinks "why should I ride this . . . bicycle, I'd rather be paralysed". Certainly many intelligent and reasonable patients have described resisted exercises with the deLorme boot as being extremely boring. They admit that they lie and cheat in a most atrocious way to avoid completing them.

At one end of the scale there is the man who has a short illness and every incentive to recover. He can be given an exercise regime that is scientifically correct. At the other end of the scale apathy and resentment may make specific exercises useless. In between these two extremes lie the majority for whom many modifications are necessary to provide greater motivation. This is done by varying the exercises; by making them have a functional significance; by group exercises; and by occupational therapy.

Three outstanding factors remain. They are all well known but are so important that they must be mentioned. These are: therapists who are enthusiastic but understanding; an optimistic atmosphere throughout the department; and a doctor who deals with his patients' fears and social problems as well as their paralysis. There is nothing better than renewed confidence for restoring a man's strength—unless perhaps it is a successful compensation claim.

Section of Endocrinology

President—A. C. Crooke, M.A., M.D.

[*May* 23, 1956]

DISCUSSION ON SOME PROBLEMS OF STEATORRHŒA AND REDUCED STATURE

Professor A. C. Frazer (Department of Medical Biochemistry and Pharmacology, University of Birmingham):

On the Growth Defect in Cœliac Disease

It is well known that a growth defect may occur in children with cœliac disease and this has been largely attributed in the past to lack of some necessary raw materials consequent upon faulty absorption. Recent studies on the ætiology of cœliac disease and other investigations have raised doubts in our minds whether this is the complete explanation of the mechanism of the growth defect. The object of this communication is to put forward an alternative concept.

Gastro-intestinal Situation in the Cœliac Syndrome

The upper part of the small intestine is abnormal in the cœliac syndrome, as shown by radiographic studies using non-flocculable opaque medium. Such studies reveal a dilated upper small intestine, devoid of the normal feathery mucosal pattern. Studies on the rate of absorption of sugars, fats, or other substances show a generalized depression and delay. In many cases the interference with small intestinal function is sufficient to cause a defect in over-all absorption. This commonly affects fat, so that the fæcal fat exceeds 5 grams a day on an average. If there is also an over-all defect of carbohydrate absorption, fermentation commonly occurs. This fermentative action results in the formation of short-chain fatty acids and alteration in bile pigments and may ultimately lead to the passage of semi-fluid, pale, bulky, foul and fermenting stools (*see* Fig. 1). In some patients there is also an increase of stool nitrogen, indicative of faulty protein absorption (Frazer, 1955).

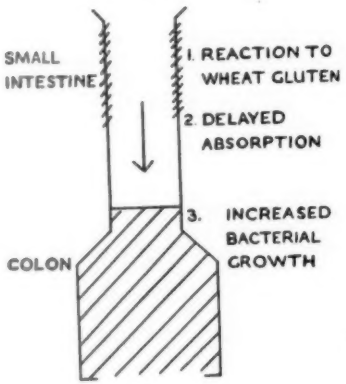

Fig. 1.—Gastro-intestinal situation in the cœliac syndrome.

Under certain circumstances, fat may be synthesized by intestinal organisms (Sammons *et al.*, 1956) and this may make a significant contribution to fæcal fat. However, we have not found these organisms to be present in the patients with cœliac disease so far examined. Labelled fat studies and other tests also indicate that increased fæcal fat is largely due to a fault in fat absorption in this condition.

Ætiology of the Enteropathy in Cœliac Disease

There can be no doubt that the enteropathy in the cœliac syndrome is induced in the great majority of cases by the ingestion of wheat protein. Following an original observation by Dicke (1950), this has been conclusively proved by van de Kamer *et al.* (1953) in Holland,

and by Anderson *et al.* (1952), Sheldon and Lawson (1952) and Ross *et al.* (1955) in this country.

At an early stage it was shown that wheat and rye protein caused deterioration in these children, but other cereal proteins did not do so. The Dutch workers obtained some slight effect with oats, but we did not find this. It was also found that complete acid hydrolysis of wheat gluten rendered it harmless to cœliac children; de-amidation with weak acid had a similar effect.

We have carried fractionation farther. Peptic and tryptic digestion appeared to be normal in cœliac children. Indeed, we have not been able to demonstrate any differences in the digestion of gluten by juices obtained from cœliac or from normal children. Wheat gluten, subjected to peptic and tryptic digestion *in vitro*, was found to be still deleterious to patients with cœliac disease. The enzymic hydrolysate was further fractionated and a water-soluble autoclaved peptide fraction was found to possess the toxic properties of the original gluten (Shaw *et al.*, 1955). Continuing farther, we have been able to show that digestion of this peptide fraction with an extract of pig's intestinal mucous membrane caused disappearance of the toxic effect. We consider that these observations show that the effect of gluten is not dependent on the presence of protein. It appears to be brought about by a glutamine-containing peptide that can be digested by pig's intestinal mucous membrane extract. The cœliac child is presumably unable to handle these peptides as effectively as the normal child. The enzymes concerned would appear to be in the intestinal wall, rather than in the juices secreted into the intestinal lumen.

Such a concept would also explain the observation of van de Kamer and Weijers (1955) that the blood of cœliac children contains a higher quantity of glutamine in bound form than that of normal children after ingestion of gluten. This effect is seen whether the cœliac child is on a gluten-containing or a gluten-free diet. We have also demonstrated a glutamine-containing peptide in the blood in a case that I propose to deal with in greater detail later. Without going farther, we may conclude that faulty handling of certain peptides in wheat gluten during their absorption is a major fault in a child with the cœliac syndrome. Since the child is normal during early infancy and apparently returns to and remains normal on a gluten-free diet, it would appear that the metabolic defect is only revealed under particular dietary conditions.

Other features of the cœliac syndrome.—In addition to this enteropathy, the cœliac child may be pot-bellied and suffer from anorexia and a variable degree of emaciation. An iron-deficient anæmia may also be present. These effects may be directly attributable to the gastro-intestinal changes, or to faulty absorption of nutrients.

However, there are other characteristic changes, the cause of which is not so easily explained. Temperamental changes are observed that change dramatically with the withdrawal or reintroduction of dietary wheat gluten—much more rapidly than the gastro-intestinal effects. Daynes (1955) has suggested that these effects may be more severe in some cases and give rise to attacks of *petit mal* and running fits. Skin lesions may be seen and there is commonly a growth defect. It is this last phenomenon that is our main concern in this paper.

The growth defect in the cœliac syndrome.—There is no doubt that a growth defect commonly occurs in children with cœliac disease. Height may be 20% or more below the normal age standard. The growth defect may result in permanent stunting. Examination of our records and the published figures of other workers (Gerrard, Ross and Smellie, 1955) shows little apparent correlation between the severity of the enteropathy and the extent of the growth defect, especially in those children in whom the gastro-intestinal changes are only moderately severe. Furthermore, the depression of growth is relieved by a gluten-free regime and re-imposed if gluten is reintroduced into the diet (Sheldon, 1955). The growth defect, therefore, appears to be an integral part of the cœliac syndrome and closely related to the primary fault. The following case rather dramatically illustrates some of the problems of the growth defect in the cœliac syndrome.

A Case of Cœliac Syndrome in which Dwarfism was the Dominant Feature

M. T. was a normal baby and she was weaned without apparent difficulty. Her childhood was uneventful, but she has suffered from nocturnal enuresis since infancy. Apart from one attack of diarrhœa at about 6 years of age and a very occasional loose stool, she had shown no signs or symptoms of gastro-intestinal dysfunction. Her parents gradually became concerned about her slow rate of growth from the age of 8 years onwards. Her mental development was normal and she did well at school. She was brought to Dr. A. C. Crooke because of lack of growth and development at the age of 13½ years. On finding no basic endocrinological abnormality, Dr. Crooke referred her to us, for investigation of gastro-intestinal function and nutritional status.

Physical examination on admission to the Metabolic Unit at Little Bromwich Hospital: Her height was 127 cm. (expected height for age 160 cm.); span 134 cm.; weight 27·0 kg. She was a pleasant, bright child. Her physical structure was like that of a child of approximately 8 years of age; there

were no signs of pubertal changes. The child was anæmic. Physical examination revealed nothing further of note.

Family history.—Both her parents were healthy; mother's height (163 cm.) and father's (173 cm.) were normal. Her mother has an iron-deficient anæmia (Hb 10·4 grams%, M.C.H.C. 29·5%, M.C.V. 87 cu.μ). There are three siblings and their heights and ages are shown in Table I. One paternal aunt may have had defective growth.

TABLE I.—SIBLINGS OF M. T.

	M. T.	J.	W.	A.
Age (years)	13 6/12	11 2/12	7 7/12	4 9/12
Sex	F	F	M	M
Height cm.	127	132	118	102
% expected height ..	79	91	92	94

General pathological studies.—Blood: Examination of her peripheral blood showed a moderately severe microcytic anæmia.

Hb 9·2 grams %; R.B.C. 3,900,000; M.C.H. 23 $\mu\mu$g.; P.C.V. 32%; M.C.H.C. 28·6%; M.C.V. 80 cu.μ; W.B.C. 8,900.

Fasting serum iron: 22 μg.%. Serology: Wassermann and Kahn reactions negative. Mantoux test 1 : 10,000 positive. Radiography: Chest—small quiescent lesion at the left hilum. Blood biochemistry: Nothing abnormal found. Parasites: No indication of infestation.

Endocrinological studies.—Bone age was normal for 13½ years.

Radio-iodine uptake was 47%, rising to 78% after thyrotrophic hormone. Ketosteroid excretion was normal and responded to adreno-corticotrophic hormone as shown in Table II. Insulin

TABLE II.—URINARY EXCRETION OF KETOSTEROIDS

Day	24 hr. vol. ml.	17-ketosteroids mg./24 hr.	17-O.H. steroids mg./24 hr.	Treatment
1	800	9	7	—
2	800	17	7	7,500 I.U. chorionic gonadotrophin
3	1230	3	7	—
4	1130	5	8	—
5	1550	16	36	ACTH 60 I.U.
6	760	15	33	ACTH 60 I.U.
7	780	18	34	ACTH 60 I.U.
8	1120	16	13	—
9	2140	10	12	—

sensitivity was normal. Visual fields were normal. Gonadotrophin excretion was less than 5 mouse units/24 hours (Klinefelter).

Gastro-intestinal studies.—Fæcal fat: Examination of serial stool samples showed that the fæcal fat was abnormal (more than 10 grams a day). Study with ^{131}I-labelled fat gave an absorption level of 82·3% that corresponded closely with the figure of 82·7% obtained from balance studies. Fæcal nitrogen and volatile fatty acids were normal.

Fat synthesis: No fat synthesizing organisms were found in the stools (Sammons *et al.*, 1956). Pancreatic enzymes (amylase, lipase and trypsin) were normal. Bile salts were normal. Radiography: gross flocculation with simple suspension of barium sulphate; non-flocculable medium showed some dilated loops of intestine. Glucose absorption curve normal. Chylomicrograph flattened.

Assessment.—Assessment of the situation at this stage indicated that this patient had some of the gastro-intestinal changes indicative of the enteropathy of cœliac disease. If so, the iron-deficient anæmia and the growth defect could be regarded as parts of that syndrome. It was, therefore, decided to examine the significance of dietary gluten in this patient.

She was placed on a gluten-free diet. Assessment of her condition was made at intervals and the main points are shown in Table III.

TABLE III.—EFFECTS OF GLUTEN-FREE DIET

Gluten-free diet	A Start	B After 47 days	C After 157 days
Mean daily fæcal fat in grams for 10 consecutive days and S.D. ..	10·5 ± 1·6	8·0 ± 1·7	4·0 ± 0·8
Blood:			
Hb gram.%	9·2	10·4	13·0
M.C.H.C.%	28·6	—	35·0
M.C.V. cu.μ.. ..	80·0	—	92·0
R.B.C. × 10^6/c.mm..	3·9	—	4·0

Growth rate	Before A	Gluten	2 months	Hospital	0	cm./month
	A to B	No gluten	47 days	Hospital	2·55	cm./month
	B to C	No gluten?	110 days	Home	0	cm./month
	After C	No gluten	23 days	Hospital	2·60	cm./month

Effect of gluten-free diet.—Fæcal fat: As shown in Table III, her fæcal fat became normal over the course of a few months, and has remained so ever since, so long as she is on a gluten-free diet.

Growth: During the two months previous to being placed on the gluten-free diet she had not grown at all. In the first forty-seven days on the gluten-free period, she grew 4 cm. During the subsequent four-month period that she was at home, she did not grow. Although she and her parents are most co-operative, it is doubted whether a strict gluten-free diet was maintained. In this connexion, it is interesting that on her readmission four months later, her fæcal fat was over 5 grams/day for three days and then came down to $4{\cdot}1 \pm 0{\cdot}25$ grams/day for the next ten days, on a strict gluten-free diet. During this period in hospital she grew at a rate of 2·60 cm./month, provided that she received no gluten.

Blood: The return of her blood picture to normal is shown in Table III.

Nocturnal enuresis: This ceased and has not recurred.

Sensitivity to gluten and gluten fractions.—It is clear, therefore, that on a gluten-free diet her whole condition showed marked improvement. It was now necessary to establish that she was truly gluten-sensitive and because of a number of differences from our usual patients with the cœliac syndrome, it seemed to us advisable to determine whether she was also reactive to our active gluten fractions. The results of some of these studies are shown in Fig. 2. They can be briefly summarized. When gluten was administered, fæcal fat changed

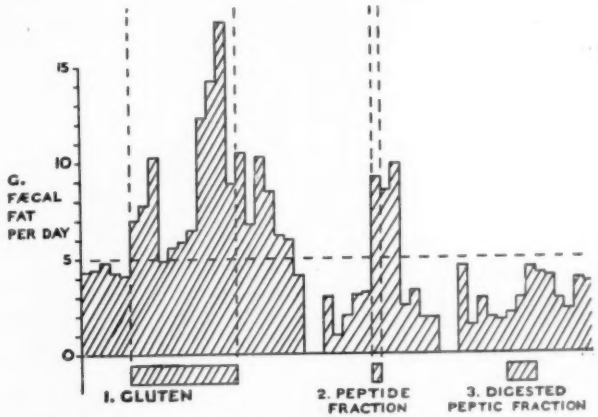

FIG. 2.—The effect on fæcal fat in gluten-sensitive patients of the administration of (1) gluten (2) peptide fraction from enzymic hydrolysate of gluten (3) peptide fraction digested with pig's intestinal mucous membrane extract.

from 4·0 grams/day to $9{\cdot}3 \pm 1{\cdot}1$ grams in consecutive ten-day periods. When the gluten was given in a single dose with fat, the fæcal fat rose to nearly 40 grams a day. This acute effect had not been seen before, but this was a new way of doing this test which is now being further investigated. In several tests, the patient was found to respond to dietary gluten changes much more quickly than most cœliac patients. From these various studies it was clear, however, that the patient was gluten-sensitive.

The glutamine-containing peptide fraction was now tested and the patient reacted to it; when this fraction was digested with pig's intestinal mucous membrane extract, no effect was produced. After the peptide fraction was administered, a glutamine-containing peptide was found in abnormally large quantites in the blood.

We, therefore, concluded that this patient has a metabolic lesion that cannot be differentiated from that of other children with the cœliac syndrome, so far as our present tests go.

To return now to a consideration of the enteropathy and the growth defect in this case:

The enteropathy during childhood was not sufficient to cause any obvious gastro-intestinal signs or symptoms. The interference with absorption mainly affected fat, there was no indication of significant interference with the absorption of protein, carbohydrate or other nutrients except iron. Even the fat absorption defect was relatively slight. However, in spite of these rather moderate changes, growth was severely affected, being more than 20% below the expected level. When placed on a gluten-free diet she rapidly grew. In the first period this was before either the enteropathy or the anæmia had significantly changed. Her increased rate of growth in this period was similar to that observed in the second period, when her enteropathy and anæmia had disappeared. It seems to us, therefore, that this patient indicates a real possibility that the growth defect in the cœliac syndrome may not be fully accounted for as secondary to material deficiencies resulting from the enteropathy. but may represent an independent effect of inadequately metabolized wheat protein.

ACKNOWLEDGMENTS

I should like to express my thanks to Dr. A. C. Crooke for permission to publish details of this patient; to several colleagues for their help, especially Dr. R. Fletcher on the clinical side, Dr. H. G. Sammons and Dr. A. A. Henly for many laboratory investigations, Miss M. Crosskey for the dietary control work, Dr. B. Shaw for preparation of the gluten fractions, Dr. J. Hoult and Dr. M. Child for the hæmatological investigations and Dr. W. R. Butt for the measurement of ketosteroids; to the Sister and Nursing Staff and the technical assistants at the Metabolic Unit, Little Bromwich Hospital, for their unfailing assistance; and to the Medical Research Council, Unilevers Limited, and the Birmingham United Hospitals Research Fund for financial support.

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Dr. C. E. Dent: *Parathyroid Adenoma with Hyperparathyroidism Developing in a Case of Lifelong Steatorrhœa.*

The case was described of a woman of 41 years with a recent history of severe bone pains and loss of height. On examination she was greatly dwarfed and she had all the biochemical and hæmatological findings of steatorrhœa except that her plasma calcium level was high instead of being normal or low. X-rays showed both osteomalacia and osteitis fibrosa generalisata. It was concluded that she was a case of lifelong steatorrhœa and had recently developed one or more parathyroid tumours and hyperparathyroidism. This was confirmed by exploration of her neck and by her response to removal of two parathyroid adenomas.

It was concluded that her parathyroid adenoma was the direct result of her lifelong steatorrhœa and that she probably passed through a phase of parathyroid hyperplasia before the two adenomas developed. Comment was made on the strange fact that her X-rays were similar to those found in some cases of chronic renal failure since they showed not only osteomalacia and hyperparathyroidism but also the "rugger-jersey" sign of osteosclerosis of the vertebral bodies. This case, together with another case of steatorrhœa showing parathyroid hyperplasia, is reported in detail by Davies *et al.* (1956).

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Professor F. T. G. Prunty: This case of Dr. Dent's is extremely interesting to us, raising as it does the question of the interrelation of osteomalacia and the subsequent development of secondary hyperparathyroidism. Good documentation of this condition is very scanty and I would, therefore, like to mention a further example seen several years ago. A man aged 35 had a ten years' history of steatorrhœa and presented three independent lines of evidence of the co-existence of osteomalacia and hyperparathyroidism. Firstly the serum chemistry showed calcium 8 to 9 mg.%, phosphorus 1·6 to 2·1 mg.% and an extremely high level of alkaline phosphatase of 78 to 97 units. Secondly, X-rays showed typical hyperparathyroid appearances in the skull, jaw and hands, together with considerable generalized decalcification and Milkman's fractures. Thirdly, bone biopsy showed a combination of areas with increased osteoid seams and areas of considerable osteoclast proliferation. Direct examination of the parathyroids was not made as it was assumed they were likely to be hyperplastic. The occurrence of an adenoma in the parathyroid in Dr. Dent's patient is particularly worthy of note.

[*June* 27, 1956]

DISCUSSION ON THE FUNCTIONAL ACTIVITIES OF THE BASOPHIL CELLS OF THE PITUITARY GLAND

Hyalinization and Basophil Adenomata in the Pituitary Gland

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THE object of this paper is to summarize the present state of knowledge concerning the conditions which give rise to hyalinization of basophil cells and to the formation of basophil cell adenomata in the rat pituitary. The hyalinization and basophil adenomata which are found in the human pituitary in cases of the Cushing syndrome will be discussed in the light of the implications of the observations which have been made in the rat.

Three types of basophil cell in the rat.—In the pars distalis of the rat pituitary there are three types of glycoprotein-containing cell, each type containing a specific glycoprotein in the form of cytoplasmic granules which are considered to be the storage form of one or other of the three glycoprotein hormones—thyrotrophin, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). The names "thyrotrophs", "FSH cells", and "LH cells" have been given to these specific cell types, each of which is considered to be concerned exclusively with the secretion of its appropriate hormone (Purves and Griesbach, 1951, 1954). Since the glycoprotein granules of all three types in the rat pituitary stain blue with about the same intensity by trichrome staining methods, they were, in the period before their diversity was recognized, referred to collectively as "the basophil cells".

Hyalinization in basophil cells.—In certain mammalian species, including the rat, rabbit, dog and opossum, the occurrence of hyalinization is observed in basophils during states of high secretory activity such as occur particularly after castration or thyroidectomy. Such changes cannot be regarded as being primarily degenerative since they also occur under normal physiological conditions as, for example, in the opossum (*Didelphys virginiana*) at the time of onset of gonad maturation (Wheeler, 1943).

Electron-micrograph studies.—The electron-micrograph studies of Farquhar and Rinehart (1954*a*, *b*) on the rat pituitary show that the basophil cells contain small ovoid vesicles. It is in these vesicles that hyaline accumulation primarily occurs. The large hyaline-filled vesicles which are observed in the rat basophils in the later stages of hyalinization are formed by a secondary coalescence of these small vesicles to form large spaces.

Hyalinization after thyroidectomy.—Hyalinization occurring in the rat pituitary after thyroidectomy affects only the thyrotrophs. These cells undergo almost complete degranulation in the first forty-eight hours after thyroidectomy, and thereafter enlarge rapidly. Hyalinization is observable as early as six days after thyroidectomy and takes the form of a large number of small hyaline-containing vesicles which subsequently undergo distension and coalescence until three or four large, irregular, thin-walled, hyaline-filled spaces result (Purves and Griesbach, 1956*a*).

Hyalinization of thyrotrophs after exposure of rats to cold.—In rats exposed to a temperature of 4° C. for fourteen days, a small proportion of the thyrotrophs show an annular zone of small hyaline-filled vesicles with retention of specific glycoprotein granules both at the periphery and in the central cytoplasm. Such cells are strongly reminiscent of the Crooke's cell of the human pituitary (Fig. 1).

Hyalinization after castration.—Hyalinization occurring in the rat pituitary after castration affects both the FSH and LH cells. Hyalinization of these cell types is relatively slow in development and the large hyaline-filled vesicles of the typical "signet-ring" castration cells are seen only eight weeks or more after castration. The unhyalinized cytoplasm contains a strong accumulation of glycoprotein granules with the staining properties of the normal specific granules of FSH and LH cells. The glycoprotein content is related to the hormone content which increases up to four months after castration (Purves and Griesbach, 1955).

Basophil cell adenomata in the rat.—Adenomata appear in the pituitaries of a high proportion of rats after continuous thyroxine deficiency of more than eighteen months' duration. These adenomata are pale in sections stained by any method, but the cells contain small amounts of a glycoprotein which stains in a similar manner to that in the normal thyrotrophs. Evidence for the view that such adenomata are derived from thyrotrophs and are induced by a long-continued stimulation of these cells has been summarized

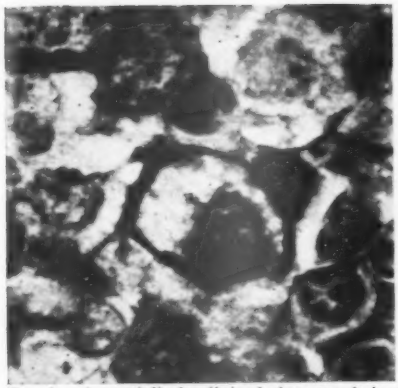

FIG. 1.—A partially hyalinized thyrotroph in the pituitary of a rat exposed to cold. The hyaline is present in small vesicles. Glycoprotein granules are present at the periphery of the cell and in the cytoplasm near the nucleus. PAS and hæmatoxylin. × 1,500.

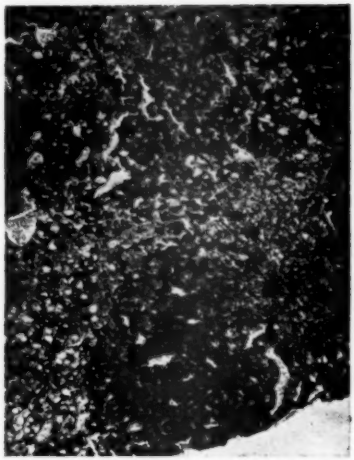

FIG. 2.—Section of a rat pituitary fifteen months after castration showing two adenomata composed of cells giving a strong reaction for glycoprotein. PAS and hæmatoxylin. × 60.

by Bielschowsky (1955). The cells of the adenomata do not show any of the hyalinization changes which affect the majority of the thyrotrophs in the surrounding anterior lobe tissue.

Until recently it appeared that castration in the rat did not give rise to basophil cell adenomata. The failure to observe adenomata after castration does not indicate any special resistance of the gonadotrophic basophils to long-continued stimulation, since, usually, the activation of these cells by castration continues at a high level for only about four months, after which the cells revert to an inactive state (Purves and Griesbach, 1955). However, in rats which are castrated at an early age this regression of the castration cells is not observed and adenoma formation occurs fifteen months or more after castration in a high proportion of animals (Houssay *et al.*, 1955; Purves and Griesbach, 1956*b*). Adenomata may also develop under certain conditions in animals which are castrated after sexual maturity since Griesbach and Purves observed such tumours in 7 out of 8 rats which were castrated at 9 months of age and examined twenty-seven months later. These adenomata often contain glycoprotein in amounts which confer strong staining properties as shown in Fig. 2. The cells of some adenomata are distinctly abnormal but in others the cells strongly resemble the normal active FSH or LH cell. It is noteworthy that the cells of the adenomata do not show any hyalinization.

The glycoprotein-containing cells in the human pituitary.—Surgically-removed pituitary tissue and fresh post-mortem material fixed in formol-Zenker have yielded sections more suitable for cytological study than the usual post-mortem material. In such sections three types of cell containing glycoprotein granules may be seen after PAS staining. These cells appear to correspond to the "beta", "delta", and "gamma" cells described by Romeis (1940). In sections stained by the Azan method or by Crossman's (1936) modification of the Mallory stain, the "beta" cells are red or purple, the "delta" cells are blue, while the "gamma" cells are only faintly stained. Contrary to Romeis, I have not found resorcin-fuchsin of value in the differential staining of "beta" and "delta" cells in the human pituitary.

Hyalinization and basophil cell adenomata in the human pituitary.—Crooke (1935) described hyalinization of basophil cells in the human pituitary in the Cushing syndrome. The typical Crooke's cell shows a hyalinized zone with retention of specific granules in the unhyalinized cytoplasm at the periphery of the cell or adjacent to the nucleus. The staining reactions of these granules are typical of those of the human "beta" cells from which the Crooke's cells are evidently derived. The fate of the "delta" and "gamma" cells in the Cushing syndrome is uncertain since these cells are not well preserved in the usual post-mortem material. The edge of the hyalinized zone in Crooke's cells shows a fine vesicular structure, in consequence of which the hyaline zone appears less sharply limited than in the mature hyalinized cells of the rat pituitary and has a ground-glass

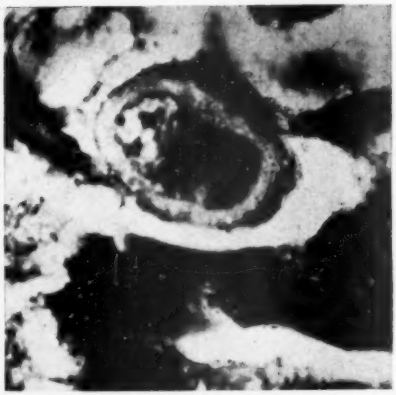

FIG. 3.—A Crooke's cell in the human pituitary. The annular zone of hyalinization shows a finely vesicular appearance. Glycoprotein granules are retained at the periphery and near the nucleus. PAS and hæmatoxylin. × 1,500.

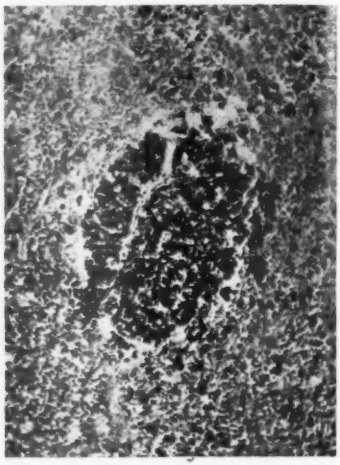

FIG. 4.—The small basophil adenoma shown here was present in the pituitary from which Fig. 3 was taken. The adenoma cells contain a heavy accumulation of glycoprotein granules here stained by aldehyde-fuchsin. AF. × 60.

appearance instead of the clear glassy appearance of the hyaline in the latter (Fig. 3). Apart from this minor difference the process appears to be the same in both species.

The basophil adenomata which are frequently found in association with hyalinization in the pituitaries of cases of the Cushing syndrome are composed of granulated cells with the staining reactions of normal human "beta" cells. As with basophil adenomata in the rat pituitary, the cells of the adenomata usually are not affected by the hyaline changes which affect the scattered "beta" cells of the pituitary in such cases (Fig. 4). This association of "beta" cell adenomata with "beta" cell hyalinization is presumably the result of a prolonged state of secretory over-activity in the "beta" cells. These changes are apparently the result of the action of excess adrenocortical secretion on the human pituitary. They do not seem to be related to excess corticotrophin secretion since they are found in cases of the Cushing syndrome which are due to autonomously secreting adrenal carcinoma and in which evidence of corticotrophin secretion is absent. Moreover similar pituitary changes are not seen in Addison's disease in which corticotrophin secretion is stimulated by adrenocortical deficiency. The actual hormone disturbance produced by excess adrenocortical secretion is unknown, but it is suggested that search for evidence of over-secretion of one of the glycoprotein hormones under such conditions may help in the elucidation of basophil cell function in the human pituitary.

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Dr. K. R. Thornton (Lecturer in Pathology, University of Birmingham): *The Action of ACTH and Cortisone on the Anterior Pituitary*

In 1950 Laqueur, and Golden and co-workers (1950) described hyalinization in the basophils of the anterior pituitary of patients who had received ACTH. Several workers have since shown that hyalinization, or increased basophilia and basophil degranulation, may

follow either ACTH or cortisone therapy in man, and may be produced experimentally in rats.

The nature of the hyaline change remains obscure; it has been regarded as an ACTH-storage phenomenon, and as a degenerative change in the basophils. In this paper, the results are presented of a study of the pituitary in 49 patients who had received ACTH or cortisone, particular attention being directed to factors altering the degree of basophil hyalinization.

Of the 49 patients, 30 had received cortisone only, 12 had received ACTH only, and 7 had received both drugs. The pituitary was obtained at post-mortem examination, and after fixation was sectioned at 3 levels in the horizontal plane, and stained by the Crooke-Russell modification of the Mallory trichrome and by PAS-Orange G. Changes in Mallory staining were noted in the cells classified as basophils and chromophobes; the acidophils remained unaffected. There was an increase in the number of cells containing PAS-positive granules; these were small, and in the Mallory-stained sections might resemble either basophils or chromophobes. Small numbers of hypertrophic chromophobes were seen, and PAS staining showed these to contain faint pink cytoplasmic granules and globules. Increased numbers of basophils were seen, this change being especially prominent in those patients on prolonged treatment with cortisone.

Three types of cytoplasmic alteration were seen within the basophils—clumping of the granules and reticulation of the cytoplasm, degranulation with the appearance of "ground-glass" cytoplasm, and hyalinization of part of, or rarely all, the cytoplasm.

Degranulation and hyalinization often occurred together within a cell, a very minor degree of hyalinization frequently being seen together with obvious degranulation, and when each change occurred alone within a basophil, the same areas of cytoplasm—perinuclear, paranuclear or peripheral—tended to be affected. In view of this, hyalinization and degranulation were considered together, no attempt being made to separate "hyaline" from "degranulate" cells during differential counting. The occurrence of these basophil changes were considered in relation to the type of drug, the total and daily dosage, the length of administration, and the time interval between the last dose and death.

The first group analysed consisted of those patients with intact adrenals who had received cortisone for a variety of diseases; a control series of a similar disease and age group constitution was used. No clear relationship was found between the daily or total dose of the drug, and the percentage of altered basophils; similarly, there was no correlation between the length of treatment and the percentage of altered basophils; some patients who had received prolonged cortisone therapy showed no alteration, and others who had received a much smaller dose of the drug over a shorter period of time showed extensive degranulation. There was, however, a direct relationship between the percentage of altered basophils and the interval between the cessation of treatment and death. In the patients in whom cortisone had been continued up to the day of death, there was a high percentage of degranulate and hyaline cells, the range being 5% to 90% of basophils: in the control series only 0·3% of the basophils were altered in the same way. In the group in whom cortisone had been discontinued four days or more prior to death, all, save one, showed basophil degranulation of the order of 0·3%. The single exception showed 10·5% of the basophils to be hyaline, although cortisone had been discontinued ten days before death; no explanation for this anomalous result was found.

The second group thus considered were the 12 patients who had received ACTH. For 10 of these patients, the same relationship of basophil change to the last dose/death interval held good; 2 of these 10 received only 40 units within a few hours and 50 units within two days of death respectively, and yet both showed over 5% of degranulate basophils. Two other patients had received large doses of ACTH finishing twenty-five and seventy-five days before death, yet both showed a high percentage of hyaline cells. However, the adrenal weights were 25 grams and 32 grams respectively, and it may be that a high level of endogenous cortisone secretion prolonged much beyond the cessation of ACTH therapy was a factor in maintaining basophil hyalinization.

5 patients were studied in whom cortisone-replacement therapy was given following bilateral adrenalectomy. In 2 patients in whom the operation was within two days of death, hyalinization was not seen although cortisone was continued up to the time of death. Of the remainder, 2 had survived five days and twelve days, and showed no hyalinization, and 1 had survived five days and showed 6·3% of the basophils hyaline. These results suggest that the effect on the basophils of exogenous cortisone is greatly modified by the presence or absence of the adrenal cortex.

In all patients in whom treatment was discontinued between one and four days before death, search was made for hyaline or degranulate basophils with signs of cell-death, i.e. extreme nuclear pyknosis or dissolution, fragmentation, &c. Very few of these degenerate cells were, in fact, found.

In summary, a high percentage of basophils which were degranulate or hyaline were found in patients to whom cortisone or ACTH was given up to the time of death; high percentages were found even in patients in whom the total dose had been small, of the order of 50 units of ACTH or 100 mg. cortisone, and in those in whom the duration of treatment had been less than two days. In those patients in whom treatment had been stopped before death, there was a progressive decrease in the percentage of altered basophils, although there were no signs of the death or removal of these cells. These facts suggest that degranulation and hyalinization are essentially reversible changes, that a return to normal basophil morphology begins one day after the cessation of therapy, and that this is, in many cases, complete by the fourth day. In view of this, and in view of the known identity of these labile glycoprotein basophil granules with the thyrotrophic and gonadotrophic hormones, it is possible that the basophil change represents some adjustment by these hormones to an increased level of circulatory adrenal cortical hormones.

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Professor Dorothy S. Russell (The Bernhard Baron Institute of Pathology, London Hospital):

The literature of recent years shows a remarkable concentration of attention upon the basophil cells of the pars distalis of the pituitary in respect both of their staining and functional potentialities. The periodic-acid Schiff method, applied by Pearse (1949) and the definition by him of a "mucoid series" of cells as a result, has lent further support to the view that the basophil cells (which contain PAS-positive granules) are responsible for the secretion of gonadotrophic hormones. It also appears that the tendency at present, amongst specialists in this field, is to attribute functional activity to the intermediate, finely granular PAS-positive cells rather than to the fully mature and more heavily granulated cells. Such interpretations are based, in general, upon the numerical increase of such cells in various endocrine disturbances and upon cytological manifestations of cell-activity.

The PAS method, as used by Pearse, demonstrates only one mature type of basophil cell. As modified by Wilson and Ezrin (1954) two forms of mature basophil cell can be distinguished by their staining affinities: the PAS-purple and PAS-red types. In practice such variations in staining can undoubtedly be seen in human glands but, in our experience, the colour-distinction between the two is not always easy. Since two distinct forms of mature basophil cell undoubtedly exist, as demonstrated by Halmi (1950) in the rat, using a modification of Gömöri's aldehyde-fuchsin stain, it is highly desirable that a consistent and clear picture of these types should be obtained in man if we are to progress in our knowledge of basophil-cell function. The aldehyde-fuchsin stain can be used for the human pituitary, but the results by Halmi's technique are uncontrollable. For the past year we have worked with a performic-acid modification of the method and this has yielded promising results. It can be claimed from this that the beta and delta cells, with purple and green granules respectively, are clearly distinguishable. Whether these are strictly analogous to the beta and delta cells of the rat remains to be demonstrated. This note of caution is necessary because, in applying the performic-acid modification to the rat's pituitary after castration, our results have differed from those described by Halmi.

Posterior lobe basophils.—Little attention has been given, in recent years, to the significance of areas of basophil invasion in the posterior lobe. While such areas are sometimes interpreted as the human equivalent of the pars intermedia of lower vertebrates, there are excellent reasons for rejecting this view. In the first place, basophil invasion is inconstant and unpredictable: it is hardly to be seen before adult life, it tends to increase with age, and is, in general, more obvious in the male than in the female. In any decade, however, examples are found in which it is either absent or slight. Secondly the cells constituting foci of basophil invasion are heavily granulated mature basophils. With the performic-acid modification of the aldehyde-fuchsin stain they always contain green granules in the otherwise normal pituitary. The cells of the pars intermedia in lower vertebrates are in the basophil, or "mucoid" category (Pearse, 1953), but they contain much smaller granules which have a feebler affinity for the PAS stain than the mature cells. In the human fœtus a narrow zone of similar cells is found in close relation to the posterior wall of the Rathke-pouch cleft: this appears analogous to the pars intermedia of lower vertebrates. It undergoes regression towards term and does not persist into later life. Since the pars intermedia of lower vertebrates is held to be responsible for the secretion of intermedin, or melanophore-expanding principle, and since also there has been some controversy as to whether or not this principle is the same as corticotrophin, we have

recently (Morris *et al.*, 1956) separated and assayed three different component parts of the fresh human pituitary. Areas of basophil invasion in the posterior lobe were identified and dissected out for separate assay. For comparison with this, portions of the hind part of the pars nervosa, and also of the anterior lobe, were separately collected and assayed.

The highest values for intermedin were found by Landgrebe and Mitchell (Morris *et al.*, 1956) in the anterior lobe, and there can be no doubt that this is the main site of production in the human pituitary. This then constitutes a fundamental distinction from the pituitary of lower vertebrates. In areas of basophil invasion the intermedin content is comparable. Basophil cells are therefore responsible in the human subject for the secretion of this hormone and, if our aldehyde-fuchsin stain is reliable, they appear to be delta cells. With regard to corticotrophin it was found by Morris *et al.* (1956) that the anterior lobe again yielded the highest content, but levels obtained for areas of basophil invasion tended to be lower, weight for weight. When the factor of dilution of anterior-lobe basophils by the other types of cell present is taken into account it can be concluded that corticotrophin production by the posterior-lobe basophils is of a low order. Since the values for intermedin and corticotrophin were not parallel in the different samples it appears that these hormones must be different substances. Finally, as might be expected, pieces of the pars nervosa proper contained little of either hormone. The trivial amounts present were probably the result of diffusion.

The hypothesis may therefore be submitted that the delta basophils in man are concerned with intermedin-secretion as one of their functions. On the other hand it is suggested that corticotrophin is produced by the beta basophils. Thus they are evidently implicated in disturbances of adrenal-cortical function. In Addison's disease, as is well known, the mature basophils of the anterior lobe undergo a marked numerical reduction. At the same time a number of "immature" basophils, sometimes referred to as "Crooke-Russell cells", are present; with the aldehyde-fuchsin stain these contain small purple granules and are thus of the beta series. With excessive activity of the suprarenal cortex, as exemplified by Cushing's syndrome, it is the mature beta basophils that undergo hyalinization—as seen by the residual purple granules in an otherwise hyaline green cytoplasm. But there is, in association with this characteristic change, an excess of immature cells with small purple granules, and similar cells may constitute the basophilic adenomas of this syndrome when present.

I mentioned earlier that the basophil cells of areas of posterior-lobe invasion are normally of what we call the delta type. In a case of Cushing's syndrome recently examined I found that a considerable proportion of these cells had assumed the staining character of beta cells, and had become partly hyalinized. This raises the possibility that the basophil cells may, with an appropriate stimulus, undergo mutation and that this, in its turn, represents an important shift in hormone-production.

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Dr. A. C. Crooke (Clinical Endocrinologist, United Birmingham Hospitals):

The suggestion of Dr. Purves that the hyaline material in the basophil cells represents a glycoprotein hormone like TSH or the gonadotrophins and not ACTH may be supported by some work recently described by Brown (1955) in our department. He has developed two methods for the assay of gonadotrophins in human urine. One depends on the increase in weight of the uterus of the mouse and measures total gonadotrophins. The other depends on the increase in weight of the ovary of the mouse treated simultaneously with chorionic gonadotrophin and is believed to be more specific for follicle-stimulating hormone (FSH). When the assays are used simultaneously it is possible to obtain a measure of the relative concentrations of FSH and luteinizing hormone (LH).

We have applied the assays to urine from women with amenorrhœa, before and after treatment with stilbœstrol and cortisone. The results in a small series of patients are shown in Fig. 1. The straight line at 100 represents the control level and shows the response of both assays to the urine of patients before treatment. The urine was assayed again during treatment and the black circles and hatched boxes represent the response and the 95% fiducial limits of the assays for total gonadotrophins, and the open circles and open boxes the response and fiducial limits of the assays for FSH compared with the control values.

Stilbœstrol in doses of 1 mg. per day or more depressed the output of both gonadotrophins. Doses of 0·5 mg. per day, however, increased the output of total gonadotrophins but depressed that of FSH. Cortisone, on the other hand, had the opposite effect to small doses of stilbœstrol and appears to be a stimulant of FSH production.

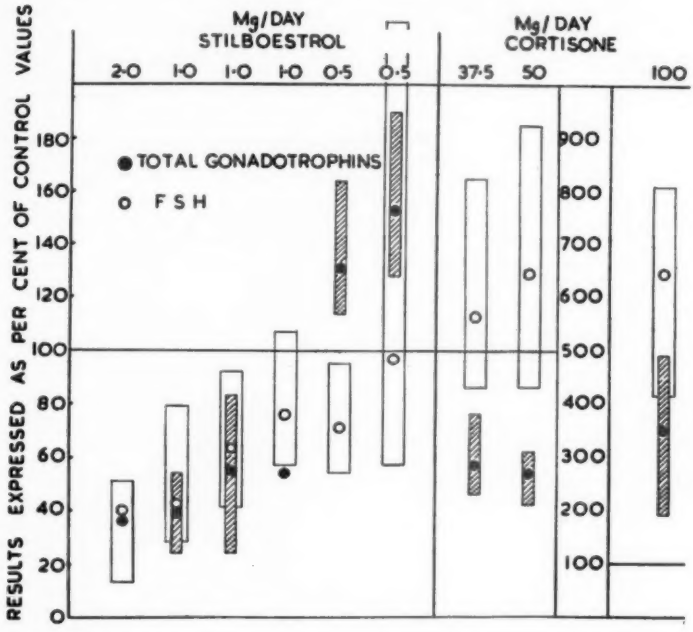

FIG. 1.—Effect of treatment on output of gonadotrophins by woman with amenorrhœa.

Now patients treated with cortisone have hyaline basophil cells in their pituitary glands, like patients with Cushing's syndrome, and it is possible that these represent some stage in the increased production of FSH reflected in our experiments.

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Section of Comparative Medicine

President—Professor JAMES MCCUNN, F.R.C.S., L.R.C.P., M.R.C.V.S.

[*May* 16, 1956]

DISCUSSION ON LEARNING IN MAN AND ANIMALS

Dr. Harry Kay (Institute of Experimental Psychology, Oxford University):

What Do We Learn?

In this paper I wish to give some idea of how one group of psychologists are working upon the problem of "What do we learn?" and the kind of answers which they are producing.

The method I am going to discuss is often referred to as a probability theory of learning; essentially the technique is to ascertain the frequency of some events and the uncertainty of others. This uncertainty can be defined technically in the language of information theory, where the information is determined entirely by the probability of an event. One binary unit ("bit") of information is the amount of information given by an event where only two things could occur; for example, would a given baby be a boy or a girl. The announcement to the new mother may be of some interest but statistically it only conveys one bit of information. (The illustration is intended to give both the limitations and the elegant neatness of the approach.) But for the psychologist the importance of information theory and similar measures of uncertainty lies not so much in the mathematics of measuring the probabilities on a relative frequency basis, for these are common enough techniques to many sciences, but rather in the way such procedures allow him to reformulate his problem. This point needs stressing because psychologists, like other scientists, are impressed by figures and the impact of information theory is often limited to considering it as a statistical procedure, whereas it would seem to me that the more significant consequence is the way it has contributed to our thinking on the importance of the perceptual aspects of a problem. We now not only have a neat statistical technique for quantifying data but by reason of it we are thinking differently about the perceptual problems in learning. In the current jargon the task is one in which so much information in the environment has to be transmitted; that is, we have so much input information on the one side, say in any given series of signals, and so much output information in the response and our task is to measure the capacity of this communication channel (which in psychology is the human subject). We do so by measuring how much information can be transmitted by such a system, or, to put it in another way, we find out what is the correspondence between the input and output messages. If a human operator is given more signals to receive than he can handle he will necessarily lose a lot of information and we can infer that the channel capacity is below that level. If he is performing to the best of his ability and can match his responses to the signals we can say this represents the channel capacity of that individual. In what ways, if any, this capacity may vary is the problem of learning. But it is important that the newness of the jargon does not blind us to the essential point—we are using a frequency measure of what information there is in a signal, we aim to say, statistically, how much a human subject can perceive and to how much he can respond. It is believed that this will give us one answer to what exactly has been learned in a particular situation.

I wish primarily to use this approach to illustrate how we can study everyday motor skills but first let us consider a few classical examples of learning. In a world of variety and change an organism has to find some measure of regularity—some measure of what is constant. Individuals can do this by several means—a popular one is that of sheer ignorance or a failure to recognize a difference. But the most common is to learn something about the environment—a person can then on the basis of past occurrences predict which event will follow another; what are the possibilities that given situation "a", "b" will follow. If he can say this, then statistically he has simplified his task, and an individual's behaviour illustrates this simplification. He does not have to look quite so hard for event "b". This is not a theoretical argument without evidence: in reaction-time experiments we find a subject can respond faster if the signal occurs during the fore-period when statistically it is most likely to happen and when a subject through his experience has learned that it will probably occur. If you prefer everyday examples there is the situation of the athlete about to start a race. Previous to getting on the track he does not start running when any gun is

fired but once he has been given the starter's "get set" he will be off if you sneeze. The information he requires at that particular point is minimal.

Let us now look at conditioning procedure—the Pavlovian case of the dog with its private dinner gong to which it salivated prior to its meal, or an individual blinking to a light flash which will be followed by a blast of air. In situations like this it seems that a subject behaves in a similar way to a conditional probability system; that is, the organism has stored some measure of how frequently one signal has been followed by another. It now responds to the first signal as if it could be taken as indicating the second. The animal does not confuse the signals—the dog no more tries to eat the bell than we attack the dinner gong. It responds to the bell not as an isolated signal but as one stimulus linked to another. The relationship —that is, the temporal and numerical relationship—between the two signals has been learned by the subject. He now knows what are the chances of one signal being followed by another and responds accordingly to them.

We can say then that the probability of the food following the bell is so great that the second event occurring after the first carries little information for the subject. He has learned how to cope with these two events by treating them not as so many independent signals but as serially dependent upon each other. There may be no particular reason why a sequence is what it is—merely that a subject's experience has shown that there is generally this serial order. But the effect of learning this regularly is to make prediction possible—a subject then is handling very little information in receiving the second event. It would seem that this conditional probability model does give us a fairly simple system for one kind of learning, and models, such as Dr. A. M. Uttley's, have illustrated its operation.

Let us now consider what appears a different operation, as in a classical experiment on attitude in recognition (Zangwill, 1937). In this situation characteristic psychological material—ink blots—was used. Subjects were asked to look in turn at six ink blots which the experimenter said would remind them of mountain scenery—they were asked to name them. Then they were shown another six blots and told these would remind them of common animals, and they were asked to name these. In general the subjects failed to notice that one of the ink blots was common to both series, and two-thirds of them happily gave it a topographical location in the first series and dubbed it an animal in the second.

In other words we have a stimulus pattern but previous experience of the subject leads him to expect, or has increased the probability of him considering, one solution in one situation and a different one in the next. The information content of the particular ink blot was identical—it was the same independent blot. But subjects responded to the situations not as one in which there were any number of equi-probable solutions, but one in which certain categories were much more likely than others. What actually has been done? The stimulus patterns have been treated as if they were presenting a lower amount of information than in fact they were. And of course this is exactly what we have to do if we are to live comfortably. It pays us to consider only a limited range of possibilities and if we don't find the answer to put up with a near miss; to be wrong a few times for the benefit of being right quickly a great many. For example we do not have to learn how to open every door when we are confronted with the handle. We depress it, and we are generally right. But what happens when the handle is in the vertical position as in the modern car. My score card says that more than half my passengers have locked themselves in when trying to get out. (This might be expected from car designers who, noticing that we have two legs, have thoughtfully provided us with three pedals.)

The subject of speech and hearing is a particularly relevant example of how we learn the probabilities of one syllable being followed by another, and come to expect certain sequences. It is not necessary, thankfully, to listen to every word I say. If we start discussing neurotic patients and clinical syndromes I can probably get away with saying "trick cyclist" when I intend to say "psychiatrist". At a broader level we do distort the evidence; we make a travesty of the input and keep our prejudices. Of course if we overdo it we land up at the Maudsley—as a patient.

This way of considering the probabilities of behaviour can be applied to many psychological experiments—say to Luchins' (1942) experiments on rigidity in problem solving, to Harlow's (1949) work on learning sets, to my own experiments (Kay, 1954) manipulating spatial proximities to vary the difficulty of a task. But I should now like to turn to what again seems a very different field of learning and one where this approach may seem less applicable; this is the field of motor skills. Let us look at an everyday example of a games player. The M.C.C. handbook regards fielding as the most natural of cricketing skills but suppose we try throwing a ball for a young boy to catch—we generally find he is far too slow in his reactions and he will let the ball hit him in the chest before he gets his hands to it. Why is he so slow? We say he doesn't *anticipate* the flight of the ball, he doesn't move himself or his hands towards it until it is too late. The youngster has to watch the ball all the way; he

never knows where it will go but only where it is. As yet he has not learned to predict. What then has he to learn to be able to predict in this situation? We may think of the trajectory of the ball as being divided up into a series of segments each of which we will call an event. An individual learns the order and temporal relationship of these events. He learns that given positions "a" and "b" the possibility of "c"—i.e. the ball at a particular point in space and time—are far greater than for "d", another such point. We might say then that given an initial series of events the individual learns which other events will occur. The skill so far is twofold—firstly, appreciating that it is a series of events and then learning to predict which series on the basis of the fewest possible initial events. Once this is done then the remaining events of the series are redundant—or at the most confirmatory. We can say, and will no doubt continue to say, that an individual *anticipates* in this situation—but strictly speaking his learning has enabled him to extract all the information from the initial events of the series, leaving the remaining redundant.

We are then putting the emphasis on the perceptual side of skills and saying that the ability to receive information would seem to be the secret of many skilled actions. Ostensibly we witness an economy and uniformity of action that is giving the exponent all the time in the world—but its basis is the expert's ability to handle both the incoming signals from the external display and the incoming signals from his own musculature. From previous learning he knows the kind of signals he is likely to receive—and given any particular one he can probably predict what will follow. By this means he is able to handle a situation in which he is literally bombarded with stimulation but whose information content is low because of its redundancy. From this standpoint the channel capacity of the skilled player has not changed from when he was unskilled. But by learning for particular contexts the frequency of certain signals and the improbability of others he is able to handle in any unit time many more actual signals. He does not receive more information. As suggested by Hick (1952) the rate of gain of information is constant but learning enables a subject to cut down the information content of the individual signals so that more can be received in a given time without increasing the information load.

The strength of this approach lies in the ease with which quantitative analysis becomes possible, but it might be argued that it is somewhat defeatist since it seems to leave out psychology. It is too preoccupied with the transmission of events and not with the system itself. Ablation studies which apparently make a direct link between performance and brain structure enjoy great prestige in psychology, and this is undoubtedly founded on the idea that with this technique the experimentalist is taking the lid off the works—the black box—and having a look inside. This then is the *direct* approach—a correlation between internal structure and behaviour. But is it? Do we in fact obtain direct evidence about the mechanism when we observe the behaviour of a damaged system? What we obtain is the same as with other observational studies—evidence from which we may or may not be able to infer the mechanism. And unfortunately, the behaviour of a mutilated system is open to a greater number of interpretations than the same behaviour from an intact system (cf. Deutsch, 1955). With animal ablation studies, where a systematic series of experiments can be conducted, and particularly where the experimenter can refer back to the performance of other intact animals, it is possible to reduce the number of interpretations. And of course if you have been wise in choosing a species such as the octopus which anatomically lends itself to ablation techniques then this further reduces some of the difficulties. But on the other hand it takes one farther from human studies, if one wishes to draw parallels.

We do, of course, get striking, even bizarre, results from ablation studies, as from other brain-damaged patients. And these have been and may be helpful in suggesting ideas about the system. I am not at all opposed to such studies but I hope I have said enough to indicate that even so-called direct methods of study may not be so direct as is often thought.

To sum up my answer to the question "What do we learn?" In many learning studies we are now putting the emphasis on the perceptual ability of the individual. The key to this perception is appreciating the relatively low information content of the incoming signals, often because they are not independent items but dependent signals within a series. In a world where so much is changing the individual finds it convenient if not essential to look for the probables and ignore the irregularities. It is therefore not surprising, but it is a little ironical that in this self-created monotone of existence an artificially created "variety" is still his "spice of life".

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Professor H. J. Eysenck (Institute of Psychiatry, Maudsley Hospital):

Modern Learning Theory

If it is agreed that the modification of the central nervous system through experience which we call "learning" is the basis of most, if not all, human and animal behaviour patterns, then it will be clear why modern learning theory occupies such a prominent part in psychology. Most influential in this connexion has been the work of Clark L. Hull, whose *Principles of Behavior* has become the classic text (Hull, 1943). The model of learning which he elaborated is a combination and formalization of two streams of thought, both of which are of considerable antiquity. One component is that of hedonism, or motivation by pain and pleasure. This was formalized and subjected to experimental study by Thorndike as the "law of effect", and now emerges under the name of "reinforcement" or "drive reduction". The other component is that of associationism; this was brought under experimental control by Pavlov and Bechtereff, in the form of conditioning or habit formation.

Hull joined these components in an impressive theoretical structure, the formal character of which makes possible large numbers of experimental predictions, many of which have been verified. This approach, it should be stressed, is a purely *molar* one; the concepts used are what psychologists call "intervening variables" or "hypothetical constructs" for which no neurological or physiological equivalent is necessarily postulated, although most psychologists would probably expect to encounter such equivalents, if only neurology and physiology were more advanced than they are (Osgood, 1953).

The most important aspect of the Hullian theory is the dissociation of performance (symbolized by Hull as $S^{E}R$) from habit (symbolized as $S^{H}R$). The letters S and R here denote stimulus and response respectively. Habit is conceived as the relatively permanent modification of the nervous system which mediates learning; the locus of this modification lies between the cortical representation of the stimulus and the cortical innervation causally preceding the response. Habits as so conceived are not directly visible or measurable; they can be indexed in terms of performance only under very special conditions. To equate habit and performance, as is often done by experimenters lacking psychological sophistication, is to invite disaster.

A very important part of Hull's work has been the elaboration of a formula linking the concepts of habit and performance. He does this by invoking another concept, namely that of drive (D). Drives in his system are the result of physiological needs such as hunger, thirst, sex, &c.; Hull takes great care in his definition of the concept of drive to avoid the many difficulties which have bedevilled the related concept of instinct.

The fundamental formula then, which links performance, habit and drive, is as follows:

$$S^{E}R = S^{H}R \times D$$

In other words, performance is a multiplicative function of habit and drive, and we can only use performance as a measure of habit if we keep drive constant. When drive is zero there is no performance, however strong the habit may be; we have many habits, but these are only translated into performance when sparked off by a suitable drive. Much experimental work has been done on the conditions determining the growth of $S^{H}R$. Among those found to be relevant are the number of reinforcements given, the nature and amount of the reinforcing agent, and the delay in reinforcement. In the studies sorting out the influence of these variables, no distinction is made between trial and error learning of the traditional kind, and classical conditioning as introduced by Pavlov; the theory is claimed to be universally applicable to all the phenomena of learning. It will be noted that among the variables determining the growth of habit, drive is not included. This is not an accidental oversight, but a part of the theoretical structure. For Hull, the amount of drive present during learning is irrelevant. This somewhat paradoxical position has been criticized, and recent experimental evidence suggests that Hull was mistaken in his neglect of drive as determining the growth of $S^{H}R$ (Osgood, 1953).

Further concepts are necessary to make this formula applicable to the majority of experimental studies. In particular, we must add the concepts of reactive inhibition (^{I}R) and of conditioned inhibition ($S^{I}R$). According to the theory, all learning, that is, all formation of stimulus-response connexions, produces some degree of inhibition or fatigue in the mediating structures; this fatigue acts as a negative drive and tends to dissipate with time during periods of rest. Such dissipation acts as a reinforcement for the prevailing state of affairs, namely, the state of rest, so that we obtain a negative habit, that is, a habit of not responding to the stimulus. Hull's general formula for performance therefore needs to be complicated

by the addition of ^{I}R and $S^{I}R$, as well as several others not mentioned in this brief summary; there is good experimental evidence in each case to support the concepts postulated, and their method of integration into the general formula.

There are other systems which also attempt to provide a formal theory for the phenomena of mammalian learning, all of which differ from Hull's in important respects. None of these, however, has been worked out in sufficient detail to generate the vast amount of detailed and precise predictions which can be made from Hull's principles. It is small wonder, therefore, that it has recently been found that no other book is quoted as frequently by psychologists in their writings as is *Principles of Behavior*. Similarly, no other system has given rise to so many experimental attempts to test its predictions, or to modify its hypotheses. While undoubtedly such experimental work will extensively modify the system, and has indeed already shown up considerable deficiencies in it, yet there seems to be no doubt that Hull has made a very great contribution indeed to psychology and has enabled us to transcend the purely empirical type of work which was so common in the first decades of this century.

The application of Hullian learning theory to the complex phenomena of social learning and psychiatry can be made in two ways. We can conceive of the symptoms shown by mentally ill people as the products of the learning process obeying the laws which Hull has laid down. A typically early example of such an application was Watson's famous demonstration of the experimental induction of a phobia in a 3-year-old boy by means of a conditioning technique. Equally, we would then think of a therapy as the removal of such symptoms and habits, also by the application of the laws of modern learning theory. Again, Watson's success in removing the phobia he had induced by means of experimental excitation may be cited as a very early example of this approach. Among psychiatrists, Wolpe (1952, 1954) of South Africa is a prominent exponent of these techniques, and his own work is in impressive confirmation of the possibilities opened up by this new approach. Here, it would seem, we have the beginning of what no other theory has ever been able to give us in the psychiatric field, namely, a *rational method of treatment based on well-known and experimentally demonstrated scientific principles* (Eysenck, 1956). Few people who have given serious consideration to this approach doubt that in due course it will oust the so-called psychotherapeutic approaches, which not only fail to be based on independently demonstrable and experimentally established general psychological laws, but which also, in spite of fifty years of extensive application, have signally failed to present any evidence of therapeutic effectiveness (Eysenck, 1952).

Another mode of application of the principles of learning theory was adumbrated by Pavlov, who suggested on the basis of systematic observations of hospitalized psychiatric patients that hysteria was due to exaggeratedly strong inhibition, while psychasthenia was due to an exaggeratedly strong excitation. As hysteria is strongly linked with extraversion and psychasthenia with introversion, this hypothesis gives us the possible basis for a typology soundly based on experimental findings. Large numbers of experiments have been done recently in an effort to investigate some of the consequences of this theory, which have been formalized and generalized by the present writer. Results have throughout been strongly favourable, leading one to the conclusion that Pavlov's long-neglected observation shows a considerable degree of insight and opens up a whole new chapter in the history of personality research (Eysenck, 1955*a*, 1955*b*).

These two applications of learning theory to psychiatry are not, of course, mutually exclusive. In line with Pavlov's hypothesis, C. M. Franks (1956) has shown that introverted neurotics, i.e. those suffering from anxiety, reactive depression and obsessional compulsive disorders, tend to condition very easily; while extroverted neurotics, i.e. those suffering from hysterical and psychopathic disorders, condition only with great difficulty. This typological and purely descriptive approach can be used in discovering the correct method of re-training a particular patient and eliminating the symptoms or habits of which he complains. (It is obvious that psychiatric symptoms in learning theory are to be classed as habits, i.e. come under the heading of $S^{H}R$; this learning theory contrasts strongly with Freud's theory, which tends to regard symptoms as symbolic activities characteristic of some purely hypothetical and ill-conceived unconscious conflict. The fact that so-called symptomatic cures can be achieved which are long-lasting and do not produce alternative symptoms argues strongly against the Freudian hypothesis.) Enuresis, tics, writer's cramp, stammer, and a variety of obscure autonomic dysfunctions have been treated very successfully by conditioning procedures, even when the patient had been treated unsuccessfully by psychotherapeutic methods for many years, but it does appear that such re-training methods are more effective in introverted people, i.e. those who condition easily, than in extroverts, i.e. those who condition more easily. In this way therapy becomes properly related to diagnosis (it is well known that in orthodox psychiatry as well as in psychoanalysis there is a very tenuous

relationship between diagnosis and treatment); thus modern learning theory provides us not only with a rational method of treatment, but also with a rational method of diagnosis.

It will be obvious to the reader that, in view of the very recent development of learning theory, its application to psychiatric problems must be in its infancy. The fact that so many promising results have already been achieved in such a short period of time, and on the basis of a very imperfect type of theory, leads us to the confident expectation that an improvement in the theory, and further research into the application of that theory to psychiatrically ill patients, will provide the great upsurge in therapeutic effectiveness which psychoanalysis originally promised to give but failed to provide.

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Section of Psychiatry

President—W. D. NICOL, M.B., F.R.C.P.

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DISCUSSION ON THE CHANGING CONCEPTION OF THE FUNCTION OF THE MENTAL HOSPITAL [*Abridged*]

Dr. A. R. May (Netherne Hospital, Coulsdon, Surrey): *The Changing Pattern of Psychiatric Care in a Mental Hospital*

Introduction.—The introduction of physical methods of treatment in psychiatry has considerably influenced the management of mental illness, although the early hopes that were pinned upon these methods have undergone some revision in the light of later experience. Any assessment of the results of physical treatment should be viewed against the background of parallel changes of administration within the mental hospital, deriving from altered attitudes to the management of psychiatric illness as a whole, during the past twenty years.

These new attitudes may be considered as due in part to a better understanding of the multifactorial basis of mental disease, and in part to the amalgamation and implementation of principles which were first put forward a century or more ago by individual pioneers. The development of these humanitarian and progressive reforms received further impetus from the provisions of the Mental Treatment Act, and with the advent of physical methods of treatment there has resulted a significant alteration in the pattern of care of mental hospital patients over the past twenty years.

The increase in admissions.—The period under review extends from 1932 to 1955 and the material is based on data collected at Netherne Hospital. This period permits a study of the background before and after the introduction of physical methods of treatment, which were fully in operation at Netherne in 1942.

The hospital was opened in 1909 and its catchment area comprises the eastern half of Surrey. The population served was approximately 800,000 until 1952, when the catchment area was reduced, and at present the number is approximately 500,000.

The total patient population was about 1,200 in 1932, rose to a maximum of 2,060 in 1946, and has now subsided to around 1,900, and this in spite of the fact that the admission rate of 1,600 is now five times what it was in 1935. There is, of course, the possibility of a change in the relative proportions of types of cases admitted in the later periods. This was suggested by the Chief Medical Officer of Health in his 1949 Annual Report as one of the factors accounting for the national increase in admission rates, and a recent study by Shepherd (1954) supports this suggestion.

Nursing staff.—The work of the mental nurse has been the subject of recent surveys undertaken in Manchester (1955) and at the Maudsley Hospital (Oppenheim, 1955). From these, it seems that apart from admission and sick wards, the time taken up in technical nursing is small and the duties of the mental nurse have not altered radically since the introduction of physical treatments. What has changed, however, is his status and also the degree of autonomy which he enjoyed twenty years ago. Bound though he was by the rules (1933) of an authoritarian regime, the mental nurse was virtually responsible for any treatment offered to the patients in his care, apart from the brief supervision afforded by the assistant medical officer on his daily visit to sign the books. The conservative attitude of some older members of the nursing staff to-day has no doubt been crystallized by this early training. Nowadays, increased medical staff has meant closer supervision, though the more permissive approach to patients has probably added to the burden of work for the nurse. At Netherne the improvement in patient–nurse ratio in 1955 (5·1 to 1 male, 7·3 to 1 female) compared with 1932 (7·2 to 1 male, 8·1 to 1 female), has been offset by the increase in admission rate.

Increase in socialization.—Recent articles in the national as well as the Medical Press (*Manchester Guardian*, 1956; Baker, 1956; Carstairs *et al.*, 1955) have renewed attention to the value of occupation as a form of therapy for mental patients, and have described the development and modification of the ideas put forward by Simon (1927, 1929). The employment of patients in various hospital departments was in operation at Netherne before 1932 when about 20% of patients were so occupied, but it was in 1936 that the first full-time O.T. staff, drawn from nurses, was appointed. At the present time some 65% of all patients resident are usefully employed either in hospital departments, in occupational therapy or on the farm and gardens; I would stress that this figure makes no allowance for the sick or senile patients, neither does it include patients who perform ward work on their own wards. If the latter are included, the employment averages 80%.

In association with the increase in employment, other trends towards socialization have

combined to alter the pattern of community life within the hospital. Chief of these was the opening of wards and the introduction of parole. In 1932, 5% of the patients were accorded this privilege within the boundaries of the estate and there were no open wards or villas. A change of policy in 1942, however, initiated a steady expansion of these numbers, and at present 60% of patients in Netherne are on parole, and 22 out of 37 wards and villas are open. The hospital has no boundary wall or fence, and patients have no cards showing them the limits of parole, which to all intents and purposes is, therefore, unrestricted.

Physical methods of treatment.—The full-scale introduction of physical methods of treatment began in 1942, although Phrenazol and prolonged narcosis were employed with a few patients from 1938.

The numbers of patients undergoing prolonged narcosis rose to a maximum of 175 in 1945 but steadily subsided to 19 in 1955. A similar decline is seen in leucotomy operations, from a maximum of 79 cases in 1949 to 19 in 1955. Patients undergoing insulin coma treatment fell from 133 in 1951 to 95 in 1955; those having E.C.T. rose to 1,200 in 1951 and numbers have fluctuated between 1,050 and 1,200 yearly since then, but it is important to realize that between 1951 and 1955 the admission rate rose from 1,300 to 1,600 and that this increase was largely composed of patients suffering from acute recent illness. E.C.T. administered to long-stay patients has, therefore, probably decreased.

Extra-mural expansion.—So far the material presented has dealt with changing conditions within the hospital. Since 1931 the contact between the hospital and the community, and consequently the selection of admissions, were influenced by the opening of out-patient clinics within the catchment area, staffed from the hospital. At present there are 4 clinics operating in general hospitals in the area.

Between 1932 and 1940 the yearly number of doctor–patient sessions varied between 100–200, but a spectacular increase began in 1941, and in 1955, 6,500 attendances were recorded at the 4 clinics. The number of new patients seen has remained at around 1,000 annually for the past ten years. (This figure does not include new cases seen on domiciliary visits.)

The foregoing details illustrate a few aspects of the changes that have arisen in this hospital during the past two decades. It would seem that the advent of physical methods of treatment coincided with an increase in emphasis on socialization, and with a more permissive attitude towards patients. In addition, there was a considerable expansion in the patient population and a marked increase in the admission rate, which may have involved some selection in the relative proportion of types of cases admitted. Brief as it is, this survey may help to illuminate the background against which one must project the results of physical methods of treatment by themselves.

The assessment of physical treatments—methods and materials.—A recent investigation at the hospital has evaluated these methods, by a comparison of the results of hospital treatment in two groups of patients, one of which was subjected to physical methods while the other was not. Readmissions were not excluded from this study.

The method of sampling was chosen to produce numerically comparable groups from two three-year periods, the first covering the years 1935 to 1937 while the second extended from July 1, 1945, to June 30, 1948. To achieve this, every other consecutive admission recorded in both male and female registers was used in the first period, and every sixth admission in the second period. In this way some 500 cases fell into each of the two samples, and the 1,000 case histories were individually examined to enable relevant data to be extracted and transferred on to specially designed cards. The information collected included age, civil and legal status, occupation, time ill before admission, previous admissions to mental hospital, duration of stay in hospital, main symptoms, treatment and diagnosis. Diagnosis presented the greatest problem as the majority of cases had been classified according to the Board of Control Schedule, but, in the main, it proved possible to reclassify the cases according to modern practice and to fit them into categories which were adapted from the International Classification of Diseases (1948). Finally, a five-year follow-up was made in each case. This involved enquiries to some 36 mental hospitals in respect of cases transferred from this to another hospital, and the despatch of approximately 500 simple questionnaires to relatives to discover whether the patient was alive and well, or had been readmitted to another hospital, or had died. A five-year follow-up was achieved in approximately 80% of both samples, which is satisfactory in view of the twenty years' interval elapsing since admission in the first sample, and, in view of the migration of population consequent upon the Second World War.

For the purposes of this present report, only part of this material is considered, namely that relating to cases of schizophrenia and the affective psychoses, and a comparison is made between those patients who received the forms of physical treatment indicated above during the first two years of their admission, and those who did not.

Comparison of samples.—The numbers of schizophrenic patients considered was 173 in

Sample I and 125 in Sample II; and of Affective Psychosis, 120 in Sample I and 83 in Sample II. There was a fall in the death rate from a total of 59 cases in the first period to a total of 15 cases in the second, and this reduction appears to be due to medical rather than psychiatric advances, as the deaths due to exhaustion and suicide remained fairly constant, at 8 in the first and 5 in the second period. Deceased patients have been excluded in calculating the significance of differences in later tables.

Inspection of the *distribution of symptoms* indicated that the loading was definitely higher in the first sample, both among schizophrenics and affectives. The most important difference among the schizophrenics was that hallucinations were recorded for 36·4% of the first sample and only 14·4% of the second sample, and this difference was very significant statistically. (Percentages are quoted for easy comparability, but statistical tests were applied to the actual numbers). Among the affective disorders, the most important difference was that in the first sample major symptoms, in addition to depression or mania, were recorded for 62·5% and in the second sample for only 45·7%, and this difference was very significant statistically.

Allowing for the fact that the first sample was a 50% one and the second a 16·67% one, the absolute number of non-hallucinated schizophrenics was about three times as large in the second as in the first. Among the affectives, allowing for the same fact, the absolute number of patients with only one major symptom was three times as large in the second sample as in the first. These figures suggest that the great increase in admissions during the second period arose largely from the admission of three times as many moderately ill patients.

The differing composition of the samples made it imperative to examine separately the hallucinated and non-hallucinated schizophrenics, and also the complicated and uncomplicated affectives, if misleading conclusions were to be avoided.

Items of comparison.—Comparison was carried out on the following items.

(1) *Status at one year:* That is Alive in Hospital v. Alive at Home; Dead being omitted.

(2) *Status at five years:* As for status at one year.

(3) *Condition after discharge:* This was assessed on the scheme suggested by Guttman *et al.* (1939) and comprises five categories, namely: Family Invalid (where the patient shows well-marked symptoms, but is manageable at home); Social Defective (where presence of minor symptoms prevents social and occupational adaptation at the previous level); Social Recovery (where there is a return to previous social and occupational level despite minor symptoms); and Total Recovery. In practice, the latter were so infrequent that Social and Total Recoveries were summated as Recovered.

(4) *Readmission rate:* This compared the number discharged and readmitted with the number discharged and not readmitted.

(5) *Time in months to first discharge:* This was taken up to five years. Patients who died without being discharged were excluded.

(6) *Total time in months in a mental hospital during first two years.*

(7) *Total time in months in a mental hospital during first five years.*

Results.—Considering first the Hallucinated Schizophrenics (Table I), there are no signifi-

TABLE I

Items of comparison	Hallucinated schizophrenics Sample I	Hallucinated schizophrenics Sample II		Non-hallucinated schizophrenics Sample I	Non-hallucinated schizophrenics Sample II	
No. alive and followed up after 5 years	48	17		100	97	
%age at home after 1 year	39·7	33·3		39	73	*
%age at home after 5 years	41·7	29·4		35	59·8	*
Condition after discharge: %age never discharged	41·8	44·4		45·2	11·2	*
Condition after discharge: %age discharged as F.I.	10·9	11·1		22·1	20·6	
Condition after discharge: %age discharged as S.D. ..	14·5	44·0	*	22·1	53·3	*
Condition after discharge: %age discharged Recovered ..	32·7	0·0	*	10·6	14·9	
%age readmitted at least once	28·1	60·0		59·3	49·4	
Mean No. months to first discharge	10·0	9·7		7·4	5·4	
Months in hospital during first 2 years	16·8	16·2		16·0	10·0	*
Months in hospital during first 5 years	34·9	38·9		37·6	18·4	*

*Statistically significant.

cant differences apart from the Condition after Discharge, which may arise as a result of applying stricter criteria of recovery in the second sample. There is a close parallel between both samples in the months spent in hospital. The evidence, therefore, is fairly strong that the treatments have no impact on the hallucinated schizophrenics. The only doubt arises from the small number of cases in the second sample, which may be too small to sustain so far reaching a conclusion.

Turning to the non-hallucinated schizophrenics (Table I), it appears that significantly

more patients in Sample II were at home after one and five years, and significantly more in Sample I were never discharged during the five years. The patients in Sample II spent significantly less time in hospital than did those in Sample I. The proportion of recoveries, however, remained about the same in both samples.

The data suggests, therefore, that the treatments have made a strong impact on the non-hallucinated schizophrenics by increasing the proportion discharged and reducing the total time spent in hospital, though not by increasing the proportion of recoveries. The most obvious interpretation is that, owing to treatment, many patients who would formerly have remained in hospital are now discharged either as Social Defectives or as Family Invalids.

The cases of Affective Psychosis are presented in Table II. Considering first those with

TABLE II

Items of comparison		Affectives with more than one main symptom Sample I	Affectives with more than one main symptom Sample II		Affectives with one main symptom Sample I	Affectives with one main symptom Sample II	
No. alive and followed up after 5 years		43	28		26	35	
%age at home after 1 year		40·9	86	*	63·2	68·2	
%age at home after 5 years		58·1	96·4	*	84·6	80·0	
Condition after discharge	%age never discharged	27·8	0·0	*	5·4	9·1	
	%age discharged as F.I.	11·1	2·9	*	13·5	6·8	
	%age discharged as S.D.	25·9	42·9	*	29·8	40·9	
	%age discharged Recovered	35·2	54·2	*	51·3	43·2	
%age readmitted at least once		28·2	22·9		34·3	65·0	*
Mean No. months to first discharge		8·4	2·9	*	8·6	4·7	*
Months in hospital during first 2 years		14·9	3·5	*	9·9	7·6	
Months in hospital during first 5 years		26·7	4·6	*	16·6	14·5	

*Statistically significant.

more than one main symptom, for example, Depression with Delusions of Guilt, it can be seen that on all items of comparison save the readmission rate there has been a significant improvement in Sample II. Treatment has enormously increased the discharge and recovery rates, and decreased in striking fashion the period of time ill.

Finally, in those cases where the main symptom was either depression or mania, it would appear that the prospects of this group are rather good without treatment and that the latter does not materially improve the situation. The fact that treatment makes little difference cannot be attributed to an uneven distribution of age groups in the two samples, as ages were closely paralleled in the two, and although the first sample had a greater proportion of manics this was not statistically significant.

Conclusion.—In conclusion, it would seem that the physical methods of treatment have had a beneficial effect in certain cases of Schizophrenia and of the Affective Disorders, but I would suggest that these results should be considered in relation to the parallel changes in the therapeutic environment of the hospital, as previously described. There is no evidence to indicate which (if either) of these factors is causal and which consequential, but together they would seem to constitute the significant alteration, during the past twenty years, in the pattern of care of the Psychiatric Patient.

Acknowledgment.—My thanks are due to Dr. J. P. S. Robertson for his assistance in the statistical analysis.

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Mr. M. S. Folkard (Netherne Hospital, Coulsdon, Surrey): *A Sociological Contribution to the Understanding of Aggression and its Treatment*

(1) *Aims of the study.*—There is an increasing recognition of the contribution which Social Science techniques can make to the social diagnosis and treatment of patients in a mental hospital. The following account is based upon the application of these techniques

to the study of a specific problem—that of aggressive behaviour in a ward for acutely disturbed female patients.

The purpose of the investigation was to study the circumstances under which aggression arises in a mental hospital ward, the problems which it presents to the nursing staff who are responsible for the care and treatment of patients, what measures could prevent or reduce the amount of aggression, and what are the most effective ways of dealing with aggression once it has arisen.

(2) *Description of the ward.*—The ward selected for the investigation was the female ward for acutely disturbed patients. There were 50 patients on the ward, most of whom had been sent there because of aggressive or antisocial behaviour. The average age was 39·7 years, with a range of 20 to 65 years, and the average length of stay in the hospital was 8·9 years, with a range of 1 to 23 years. The patients were practically all suffering from some form of chronic psychosis, there being 33 Schizophrenics, 6 Epileptics, 5 Psychopaths, 4 Manic-Depressives, and 2 Mental Defectives.

When the Investigator went on the ward in the early part of 1955 considerable changes were taking place regarding therapeutic policy and ward organization. An attempt was being made to increase the number of patients engaged in occupational and social activities, more interest was being paid to individual patients, and their needs satisfied more adequately in various ways.

(3) *Method of study.*—It was assumed that aggression may arise from multiple causes, and an attempt was made to identify individual and social variables with which it may be associated. The method of study was determined by the nature of the problem, the subjects being investigated, and the theoretical assumptions underlying the research. The data were collected during a ten-week period of study, and various techniques were used to obtain the necessary information.

The Investigator adopted the role of a full-time research worker, and in this capacity spent considerable periods in the direct observation of patients engaged in many activities both on and off the ward. It was decided to enlist the help of the nursing staff in the collection of data, and for this purpose a special form was constructed on which was recorded the data regarding various features of each aggressive act, of the circumstances of the situation in which it occurred, and of the action that was taken in dealing with it. This information was recorded by the nurse who had observed the incident as soon as possible after it had occurred. Aggression was defined in terms of overt behaviour, and was regarded as "Personal Aggression" if directed at other individuals either in the form of verbal or physical attack, and as "Impersonal Aggression" if directed at property in the form of breaking, banging or knocking things over. The recorded information referred to observed behaviour and facts, requiring no inference or interpretation. This method of data collection required training and supervision of the nurses for this purpose, and subsequent checks indicated this was a reasonably valid and reliable technique.

To obtain a classification of the patients based on general behaviour and social characteristics they were all rated on the Fergus Falls Behaviour Rating Scale as used by Lucero and Meyer (1951). This rating was performed by the two Sisters on the ward each week during the period of the investigation. Additional information was obtained from ward records and reports, ward meetings, and from formal and informal interviews with individual members of the staff.

(4) *Results.*—The records of overt aggression were analysed in relation to specific individual and social variables. It is hoped that this type of analysis will help to show those features and characteristics which tend to be most frequently associated with aggressive behaviour. Correlation may not be a sufficient condition, but it is a condition in establishing causation.

The data presented here refer to 298 acts of aggression committed by 32 out of the 50 patients on the ward during a period of ten weeks. For purposes of analysis the patients have been grouped into three main categories: firstly, those who were not aggressive, of whom there were 18 patients. Secondly, those who were fairly aggressive, having committed from 1 to 5 acts of aggression, of whom there were 18 patients. Thirdly, those who were very aggressive, having committed 6 or more acts of aggression, of whom there were 14.

The selected variables were then compared within these groups with a view to establishing the nature and extent of any association.

The χ^2 test indicated that the characteristics associated with aggressive patients, and which were significant at the 5% level, were poor co-operation with nurses and lack of parole. Other variables studied, but which did not appear significant, were—age, marital status, intelligence, diagnosis, general behaviour rating, response to other patients, work, psychomotor-activity, length of hospitalization, legal status, number of visitors, and physical forms of treatment. However, there are interesting features of some of these variables which are revealed by a more detailed consideration of the data.

(1) In the present analysis age (Table I) is not very significant, but a more detailed con-

TABLE I.—CHARACTERISTICS OF AGGRESSIVE AND NON-AGGRESSIVE PATIENTS - APRIL 10 TO JUNE 18, 1955

Variable	Number of aggressive acts: 0	1–5	6+	Total
	Number of patients			
Age				
(1) Under 40	9	8	8	25
(2) 40 and over	9	10	6	25
Marital status				
(1) Single	10	10	12	32
(2) Married	8	8	2	18
Response to patients				
(1) Rating 1+2 (low)	6	11	7	24
(2) Rating 3+4 (high)	12	7	7	26
Response to nurses				
(1) Rating 1+2 (low)	3	8	9	20
(2) Rating 3+4 (high)	15	10	5	30
Hospitalization				
(1) 0–5 years	10	6	5	21
(2) Over 5 years	8	12	9	29
Parole				
(1) No parole	4	8	9	21
(2) Parole	14	10	5	29
Work				
(1) Rating 1+2 (low)	8	11	9	28
(2) Rating 3+4 (high)	10	7	5	22
Leucotomy				
(1) Performed	3	7	5	15
(2) Not performed	15	11	9	35
E.C.T.				
(1) 0–50 treatments	11	8	4	23
(2) Over 50 treatments	7	10	10	27
Total No. of patients	18	18	14	50

sideration of the data suggests that the younger group comprises samples of two populations; one which is indistinguishable from the older group and one with a high number of incidents which has no parallel in the other group. If one considers only those patients who were responsible for 11 or more aggressive incidents, there were 7 individuals in this category, of whom 6 were under 40.

(2) Analysis of marital status is shown in Table I. 32 of the patients were unmarried, including 10 of the non-aggressive ones, but the fact that 12 out of the 14 very aggressive patients were unmarried suggests that aggression is one factor in determining whether a patient is married or single.

(3) The social response to other patients, assessed by the Fergus Falls Behaviour Rating Scale (Table I) indicates that 12 out of the 18 non-aggressive patients were given a higher rating regarding the extent to which they initiated contacts with other people.

(4) Co-operation with nurses, also assessed by the Fergus Fall Behaviour Scale (Table I), is seen to be clearly related to aggression. The most aggressive patients were also much less co-operative in general. 15 of the 18 non-aggressive patients were given a high rating, whereas 9 of the 14 very aggressive were given a low rating.

(5) When length of hospitalization is considered (Table I) it is seen that a higher proportion of those patients who were admitted six or more years ago were aggressive, compared with those who have been in the hospital for less than six years. Aggression is undoubtedly one of the main reasons for the continued hospitalization of many of these patients. However, it seems likely that this is a two-way relationship, with enforced hospitalization acting as a contributory cause of aggressive behaviour.

(6) The parole analysis (Table I) shows an orderly progression in the data, those patients having no parole being the most aggressive. In some instances the patients had lost their parole because they were aggressive, and although this was not invariably the case, there is need for caution in interpreting this relationship.

(7) The data regarding the occupation of the patients (Table I) shows that the good workers, given a high rating on the Fergus Falls Scale, comprised a smaller proportion of aggressive patients than did the poor workers. In fact 12 of the good workers were aggressive compared with 20 of the poor workers. This would suggest that employment of the patients tends to reduce the amount of aggression, but is not in itself a complete solution to the problem.

(8) Pre-frontal leucotomies (Table I) had been performed on 15 out of the 50 patients. Without more detailed knowledge of the behaviour of these patients prior to the operation it is difficult to assess any possible improvement in them. Some of them were, in the opinion of the staff, less aggressive than they had been, but the present data indicate that 7 of them are still fairly aggressive, and 5 of them are very aggressive.

(9) With regard to electrical treatment (Table I), 12 out of the 23 patients who had received up to 50 treatments were aggressive compared with 20 out of the 27 who had received more than 50 treatments. Some of the latter may be less aggressive than they had been, but 10 of them are still fairly aggressive and 10 of them are very aggressive. This suggests that electrical treatment may have been more useful as a temporary method of controlling aggression which had already occurred, rather than as a preventive measure of treatment.

The data can be analysed using not the individual, but the aggressive act as the unit of analysis. This will help to show the types of situations which most frequently give rise to aggression, and the problems which aggression presents on the ward in terms of social management. Analysed in this way, it can be shown for instance that more aggression occurs in the dining room at meal times than in any other single situation, and that there appears to be a diurnal variation, with progressively less aggression occurring over the course of the day.

(10) Ninety-one of the aggressive acts were related to particular patterns of staff-patient interaction (Table II) in 42 cases being the response to requests or instructions by the staff.

TABLE II.—TYPES OF SOCIAL INTERACTION GIVING RISE TO AGGRESSION

Staff–patient interaction		Patient–patient interaction	
Requests and instructions	42	Related to food, &c.	21
Giving attention	13	Interference	20
Restrictions	11	Criticism or abuse	20
Unsatisfied demands	11	Restless patients	18
Restraint	8	Aggressive patients	8
Related to treatment	6		
Total No. of incidents	91	Total No. of incidents	87

"Restraint" in the table refers to verbal restraint and physical intervention to separate patients, not to mechanical forms of restraint. This suggests the importance of staff attitudes and of the way in which patients are approached by the staff.

(11) Eighty-eight of the aggressive acts arose out of patient–patient interaction (Table II), which could be classified as: Related to food, drinks, sweets, and cigarettes, response to interference, response to criticism or abuse, response to noisy or restless patients, and response to aggression of other patients.

(12) The disturbance created by aggression is illustrated in Table III. There were 180

TABLE III.—DEGREE AND DURATION OF DISTURBANCE CAUSED BY AGGRESSION

Duration of disturbance	Degree of disturbance: Mild	Moderate	Severe	Total
Under 10 minutes	92	68	20	180
10 minutes to 1 hour	12	37	38	87
Over 1 hour	1	14	16	31
Total	105	119	74	298

aggressive acts which created a disturbance on the ward lasting less than ten minutes each, of which 20 were rated as severe. There were 87 incidents lasting between ten minutes and an hour each, of which 38 were rated as severe, and there were 31 incidents lasting more than an hour each, of which 16 were rated as severe. It will be seen that there is a tendency for a higher proportion of the more lengthy incidents to be also more severe. This would suggest that, in general, short temporary removal from the situation is not an adequate remedy for severe aggression, which may require different methods of treatment.

(13) Table IV indicates the types of action taken in dealing with aggression and the effectiveness of treatment. In accordance with the changed policy of treating the patients, most of the aggression was dealt with by social means rather than by physical methods of treatment. By far the most common method was to remove that patient from the situation in which aggression has occurred. It would seem that it is possible to run a ward of this

TABLE IV.—METHODS OF TREATING AGGRESSION AND EFFECTIVENESS OF ACTION TAKEN

Action taken	Effect of action taken: None	Slight	Good	Total
None	5	11	13	29
Restraint	5	18	18	41
Removal from situation ..	14	62	81	157
Bed	2	10	26	38
Sedation	3	12	13	28
E.C.T.	—	—	1	1
Seclusion	—	4	5	9
Total	29	117	157	303

description without the extensive use of sedation, E.C.T., and seclusion, but this depends on meeting the needs of individual patients more adequately and hence reducing the frustrations and provocations which lead to aggression. It depends also upon the development of appropriate staff attitudes, which are probably the most important factors in dealing with the problem.

It is suggested that investigations of this nature can contribute to the social diagnosis and treatment of patients, and assist in the development of a more constructive policy of ward management.

REFERENCE.—LUCERO, R. J., and MEYER, B. T. (1951) *J. Clin. Psychol.*, **7**, 250.

Dr. R. K. Freudenberg, and **Dr. J. P. S. Robertson** (Netherne Hospital, Coulsdon, Surrey):

Personal Stresses in Relation to Psychiatric Illness

PERSONAL stresses, defined as experiences and circumstances, that may have an adverse effect on an individual's behaviour, were examined with the help of a social schedule (Freudenberg *et al.*, 1956) in two groups of psychiatric patients, one comprising admissions under 60 and the other consisting of 100 consecutive admissions over 60. Both psychiatric groups were compared with controls: those under 60 with admissions to a general surgical ward and a neurosurgical unit; psychiatric patients over 60 with members of a near-by Darby and Joan Club without psychiatric disability. These stresses were investigated to elucidate their relation to psychiatric diagnosis and treatment responses. Such a study should also elucidate psychotherapeutic and other social measures used in psychiatric practice.

"The general point of view is that an individual must be seen simultaneously as an organism, a member of society, and a personality in a culture. These three dimensions with their various potentialities for stress and strain affect human life both in health and illness" (Simmons and Wolff, 1954). In the present investigation only the incidence of personal stresses was ascertained. The complexity of the problem and various methodological difficulties and deficiencies impose limitations which will allow only tentative conclusions. The present investigation is therefore only a contribution and not a final answer to the problem.

Psychiatric patients under 60.—The investigation into this group, without the control comparisons, has been published elsewhere (Freudenberg *et al.*, 1956). Subsequently the following additional comparisons were made for each of the 91 personal stresses: A. Incidence of total number of stresses in the various diagnostic groups versus control (Table I). B. Incidence of separate stresses in various diagnostic groups versus control (Table II).

TABLE I.—TOTAL NUMBER OF STRESSES

Group	N	Mean	Range
Control	50	11·9	3–23
Schizophrenic ..	51	15·1	2–29
Depressive	19	11·3	3–25
Psychoneurotic ..	23	13·7	2–29

Analysis of Variance. F ratio = 3·276, df. 3 by 139.
Significant at 5% level.

A. Incidence of Total Number of Stresses in the Various Diagnostic Groups Versus Control (Table I)

Analysis of Variance: F ratio = 3·276, df. 3 by 139.
Significant at 5% level.

Examination of the means by the fiducial limits technique indicates that the significant difference operates between the controls and the depressives on the one hand and the schizophrenics on the other. The psychoneurotics do not definitely differ from either.

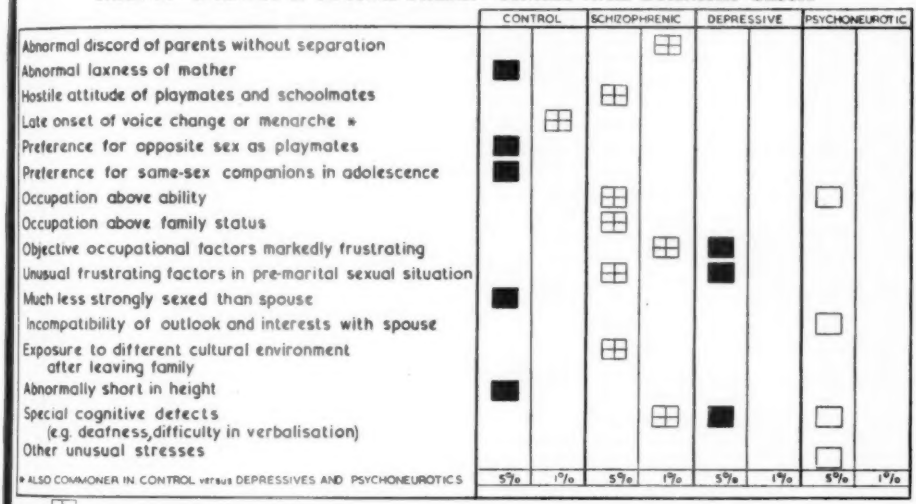
Table I shows the total number of personal stresses in the diagnostic groups versus non-psychiatric controls. N gives the number of patients.

It will be seen that the mean incidence is highest in schizophrenics. The incidence in depressives is significantly lower than in schizophrenics and does not significantly differ from controls. The psychoneurotics seem to occupy an intermediate position between controls and schizophrenics but do not definitely differ from either. This may suggest that the highest number of stresses is related to the severest disorder, schizophrenia.

Both samples, control and diagnostic groups, were investigated by the same person (Psychiatric Social Worker).

B. Incidence of Separate Stresses in Various Diagnostic Groups Versus Control (Table II). Table II shows the significant separate stresses in the various diagnostic groups versus the non-psychiatric control.

TABLE II.—INCIDENCE OF PERSONAL STRESSES—CONTROL *versus* DIAGNOSTIC GROUPS



The following comparisons were made and the significant stresses indicated by: black squares signifying the comparisons between depressives and controls, white squares crossed with black the comparison between schizophrenics and controls and the white squares those for the neurotics and controls.

It will be seen that the stresses found significant were present largely in the sections of Childhood in General and only some under Occupational and Sexual and Marital stresses. None were found significant in Earliest Childhood.

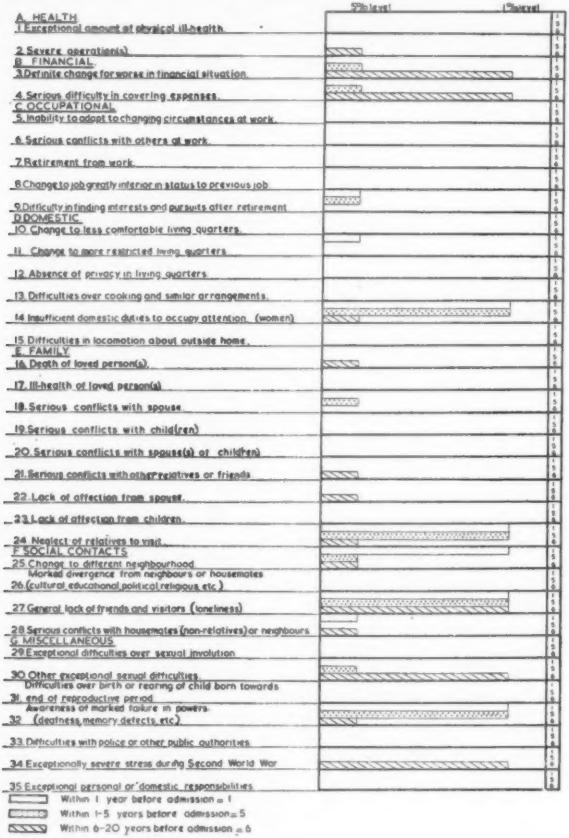
To pick out only a few: in schizophrenics there was a significantly higher incidence of abnormal discord between parents without separation (1%) than in controls. Objective occupational factors were more frequently markedly frustrating (1%). It is, of course, impossible to say what is causal and what consequential from such findings.

Personal stresses were more frequent in the psychiatric group than in controls, i.e. 10·9 significant differences could be expected by chance at 5% level but 18 were actually obtained; 2·7 significant differences were expected at 1% level and 6 were actually obtained.

The incidence of significant differences between controls and psychiatric groups was low in Earliest Childhood, was above chance in Childhood in General, Occupational, Sexual, Marital and Miscellaneous stresses.

Patients under 60: *conclusions.*—The investigation referred to above revealed that personal stresses in psychiatric patients under 60 years of age where no significant differences could be found included many to which great importance is often attached. This finding was further reinforced by the comparisons with the control group where bottle feeding, weaning difficulties, lax toilet training, strict toilet training, late establishment of bowel control, unusual feeding difficulties, over-affection from mother, early death of mother or father, separation from mother while under the age of five, &c., were not found to be significantly greater in incidence in the psychiatric group as compared to controls.

TABLE III.—SIGNIFICANCE OF PERSONAL STRESSES—SENILE *versus* CONTROL



The significant findings as evident from Table II will repay further investigation. The number of stresses experienced is apparently related to the most marked behaviour disorder. The incidence is highest in schizophrenia. In depressives the incidence is lower and does not differ significantly from controls in contrast to schizophrenics where the incidence is definitely higher than controls. This may indicate that existing genetic and constitutional factors are more important for the development of a depressive illness.

The significant differences in separate stresses experienced by patients under 60 compared to controls seem to justify attempts to modify the stimuli of the environment or the experience of it by psychological, sociological and/or physical therapy, particularly as long as we have not definitely discovered what genetic or acquired factors are causative in the promotion of any pathological behaviour in spite of the fact that only moderate importance can probably be attached to them. The stress sections where the present investigation suggests that this may be rewarding are: Childhood in General—particularly parental attitudes; occupational problems; sexual and marital problems; and other various adult stresses.

Psychiatric patients over 60.—The second sample in which personal stresses were investigated consisted of 100 consecutive female admissions over the age of 60 where no previous hospital treatment had occurred.

Roth (1955) has shown that the five senile psychotic groups: (1) affective psychoses, (2) senile psychoses, (3) late paraphrenias, (4) acute confusions, and (5) arteriosclerotic psychoses are each characterized by a distinctive pattern of natural history. He suggests that, apart from biochemical and physiological differences, there might also be psychological and environmental factors which "are unlikely to be of equal importance in these five groups so markedly different in natural history".

For the senile group another check list of 35 items was compiled, divided into three periods: one year before admissions; one to five years before admission; six to twenty years before admission.

Senile patients were divided into diagnostic groups as suggested by Roth:

Senile dementia	21
Arteriosclerotic dementia ..	25
Paraphrenias	11
Confused patients	4
Affective psychotics	34

5 cases were omitted as 3 had been in-patients in mental hospitals before the age of 60 and in 2 cases histories were not available.

The same check list was used for 100 females aged 60 and over attending near-by Darby and Joan Clubs without any evident psychiatric disability.

Mean age of senile group=72·8 (range 60–94)
Mean age of control group=72·3 (range 60–90)

The following differences were statistically significant:

Total Stresses: Senile Versus Controls

More frequent in total groups of Seniles (*Table III. Significance of personal stresses. Senile v. Control*)

Table III shows the separate significant stresses in the control group of non-psychiatric old people over 60 versus the total senile psychotic sample.

On the left the social schedule with its various sections: Health, Financial, Domestic, Family, Social Contacts and Miscellaneous. On the right are the significance levels, 5% and 1%.

To mention only a few of the significant differences at 1% level more frequent in senile psychotics: a definite change for the worse in their financial situation; insufficient domestic duties to occupy attention; general lack of friends and visitors. These alone already suggest worth-while social therapeutic measures.

Senile control and senile psychiatric sample was in this case investigated by a different person, which may have influenced the results.

Total Senile Versus Control Comparisons: Chance Expectancies and Actually Obtained (Table IV)

Table IV.—Senile *versus* Control

Comparisons= 35 stresses × 3 periods
= 105

Level %	Expected by chance	Actually obtained
5	4·20	18
1	1·05	13

Table IV shows that there occurred more significant differences between seniles and controls than would be expected by chance.

Table V gives the total actual number of stresses in the separate diagnostic groups and in control.

Table V.—Senile Investigation Total Stresses: Seniles and Controls

Group	*Summary* N	Mean	Range
Controls	100	5·1	0–13
Senile dementias	21	7·5	2–15
Affective psychoses	34	8·3	2–23
Arteriosclerotics	25	9·6	5–18
Paraphrenics	11	9·6	5–14
Confusional	4	11·2	7–14

Analysis of Variance. F ratio=12·33 d.f. 5 by 189. Significant well beyond the 1% point.

The controls show a distinctly lower incidence of stresses than all other diagnostic groups except the senile dements. The senile dements are distinctly lower than confusionals, but with all others there appears to be no significant difference in incidence. These differences if confirmed in another sample are highly suggestive.

Next, comparisons were made between the incidence of personal stresses in relation to the five diagnostic groups irrespective of controls.

INCIDENCE OF PERSONAL STRESSES IN RELATION TO DIAGNOSIS IN SENILES (TABLE VI)

Table VI shows the separate stresses significant at 1% and 5% levels in which the diagnostic groups differ from each other.

TABLE VI.—INCIDENCE OF PERSONAL STRESSES IN RELATION TO DIAGNOSIS IN SENILES

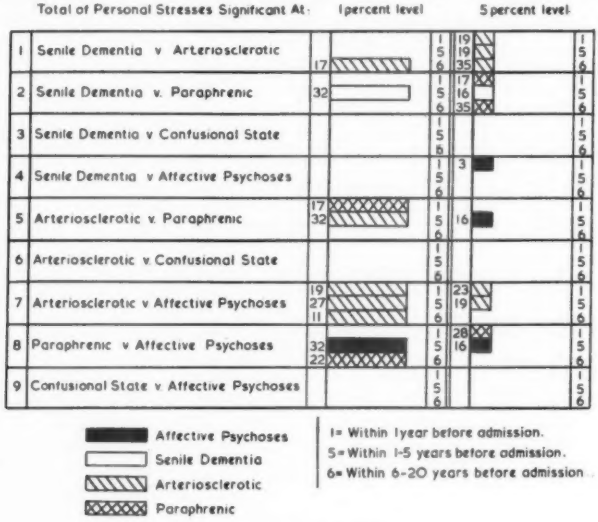


TABLE OF PERSONAL STRESSES

3 Definite change for worse in financial situation.
11 Change to more restricted living quarters.
16 Death of loved person(s).
17 Ill-health of loved person(s).
19 Serious conflicts with children.
22 Lack of affection from spouse.
23 Lack of affection from children.
27 General lack of friends and visitors (loneliness).
28 Serious conflicts with housemates (non-relatives) or neighbours.
32 Awareness of marked failure in powers (deafness, memory defects, etc).
35 Exceptional personal or domestic responsibilities.

Diagnostic comparisons 1–9 on the left.

It is of interest to see how frequently significant differentiating stresses occur as commoner in the arteriosclerotic group (white with black oblique line) as compared to the other diagnostic groups, which is suggestive that conflict may have some relation to the development of hypertension and arteriosclerosis in liable subjects.

Table VII gives the separate stress incidence for diagnostic comparisons split up into the various sections of the social schedule.

TABLE VII.—SENILE INVESTIGATION

Stresses: Expected and obtained significant differences
Senile Dementia v. *Arteriosclerotics* v. *Affectives* v. *Paraphrenics*

Section	No. of comparisons	Expected 5%	Expected 1%	Obtained 5%	Obtained 1%
Health	36	1·44	0·36	0	0
Financial	36	1·49	0·36	1	0
Occupational ..	90	3·60	0·90	0	0
Domestic	108	4·32	1·08	0	1
Family	162	6·48	1·62	6	4
Social contacts ..	72	2·88	0·72	1	1
Miscellaneous ..	126	5·04	1·26	2	3
Total	630	25·20	6·30	10	9

The total number of significant differences was found to be below expectancy at 5% level Under individual sections the incidence of significant differences under Family and Miscel-

laneous Stresses such as Exceptionally Severe Stress during World War II was above expectancy by chance. This is again suggestive.

SENILE INVESTIGATION: SIGNIFICANT DIFFERENCES EXPECTED AND OBTAINED DIFFERENCES. TOTAL COMPARISON OF (1) DIAGNOSTIC GROUPS AND (2) PROGNOSIS (TABLE VIII)

TABLE VIII.—SENILE INVESTIGATION

Stresses: Expected and obtained significant differences

Total Comparisons 1. Diagnostic Groups
2. Prognosis

Comparisons	No. of comparisons	Expected 5%	Expected 1%	Obtained 5%	Obtained 1%
1. *Diagnostic Group*					
Senile Dementias v. Arteriosclerotics	105	4·20	1·05	3	1
Senile Dementias v. Affectives ..	105	4·20	1·05	1	0
Senile Dementias v. Paraphrenics ..	105	4·20	1·05	1	1
Arteriosclerotics v. Affectives ..	105	4·20	1·05	2	3
Arteriosclerotics v. Paraphrenics ..	105	4·20	1·05	1	2
Affectives v. Paraphrenics ..	105	4·20	1·05	2	2
2. *Prognosis*					
Alive v. Dead Senile Dementias	105	4·20	1·05	2	0
Not dis. v. dis. Arteriosclerotics	105	4·20	1·05	1	0
Not dis. v. dis Affectives ..	105	4·20	1·05	5	3
Not dis. v. dis. Paraphrenics ..	105	4·20	1·05	0	0
Total	1,050	42·00	10·50	18	12

Table VIII shows the total number of significant differences expected by chance and actually obtained: (1) in the diagnostic comparisons; (2) in relation to response to treatment.

TABLE IX.—INCIDENCE OF PERSONAL STRESSES IN RELATION TO PROGNOSIS

Dead and still hospitalised versus Discharged

Personal Stresses more frequent in Dead and still hospitalised	AFFECTIVE PSYCHOSES
Change to less comfortable living quarters within 1 year before admission	—
Change to less comfortable living quarters within 1-5 years before admission	—
Insufficient domestic duties to occupy attention within 1 year before admission	—
Absence of privacy in living quarters within 1 year before admission	—
Absence of privacy in living quarters within 1-5 years before admission	—
Severe operation(s) within 6-20 years before admission	—
Serious conflicts with housemates (non-relatives) or neighbours within 1 year before admission	—
SIGNIFICANT LEVEL	5% 1%

It indicates that, if one goes into further detail, certain individual comparisons show a higher incidence of differentiating stresses than expected by chance.

The highest incidence of differentiating stresses occurred in the Arteriosclerotic group.

Differences in the incidence of stress are also apparent between Discharged versus Not Discharged Affectives.

The total of significant differences in stresses in the diagnostic comparisons expected at 5% level is definitely below expectation, but those at 1% are slightly above.

Incidence of Personal Stresses in Diagnostic Groups in Relation to Treatment Response or Prognosis (Tables IX, X)

Table X.—Senile Investigation

Stresses: Expected and obtained significant differences
Response in Groups Dead v. Alive Senile Dementias
Non-Discharged v. Discharged Others

Section	No. of comparisons	Expected 5%	Expected 1%	Obtained 5%	Obtained 1%
Health	24	0·96	0·24	2	0
Financial	24	0·96	0·24	0	0
Occupational ..	60	2·40	0·60	0	0
Domestic	72	2·88	0·72	2	3
Family	108	4·32	1·08	1	1
Social contacts ..	48	1·92	0·48	1	0
Miscellaneous ..	84	3·36	0·84	1	0
Total	420	16·80	4·20	7	4

Table IX shows the incidence of separate stresses in relation to treatment response or prognosis. The incidence of separate stresses is compared between Dead and Still Hospitalized and Discharged Affective Psychotics.

It is evident from the table that: Change to less comfortable living quarters, insufficient domestic duties or lack of privacy in living quarters are more important factors for lack of response to treatment than mere personal stresses.

Table X again gives the total of significant differences in treatment response comparisons as expected by chance and actually obtained, split up into sections. It confirms that domestic problems obtained frequencies above expectancy by chance for Affective Psychoses. The other main problems seem to centre round physical health.

In the discharged Affective Senile Psychotics, ill-health of loved person was significantly higher in incidence one to five years before admission.

Patients over 60: *conclusions.*—The total number of stresses in the senile diagnostic groups versus controls showed that the controls have a distinctly lower incidence as compared to all diagnostic groups except the Senile Dements. The most likely relationship is again that the other groups like Paraphrenics, Confusional States and Arteriosclerotic Dementias would, on the whole, show a more severe behaviour disorder than the mere Senile Dements.

In the senile groups, stresses seem to have a more important differing incidence between diagnostic groups and also in the treatment response comparisons. This occurred particularly in the sections concerning physical health and domestic problems, such as restricted living quarters.

General Conclusions

Our findings are in agreement with the evolutionary theory of disease which regards illness as inherent in the nature of life itself and as arising either from the universal preying of one species on another or from genetic variability, or from environmental circumstances which the organism's inherited structure is unable to resist.

"The complex relation of personal stress and illness can only be further elucidated with more refined methods which would bring more detailed and systematic knowledge of the existing social context and the particular person involved" (Simmons and Wolff, 1954).

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Section of Medicine

President—G. E. BEAUMONT, M.A., D.M., F.R.C.P., D.P.H.

[*April* 24, 1956]

DISCUSSION ON SARCOIDOSIS

[Continued from October *Proceedings*, page 808]

Dr. A. H. T. Robb-Smith:

The Pathological Aspects of Sarcoidosis

For the pathologist, there are three questions to be answered in considering Sarcoidosis:

(i) Is sarcoidosis a disease entity or a symptom complex?

(ii) If it is a disease entity, what are its morphological characters and what part can the laboratory play in revealing the diagnosis?

(iii) What is the nature of the disease process and, still more difficult, what is its ætiology?

The majority of observers would accept sarcoidosis as a disease entity, although there is unlikely to be agreement on a satisfactory definition and, as inevitably occurs in diseases of unknown ætiology, the nosological frontiers beyond which a case ceases to be an "atypical" example of sarcoidosis are ill-defined. Pautrier wrote of the danger of including cases with atypical features and ambiguous histological structure, lest the disease becomes a "formless monster without limits". The answer to the second question is that the morphology of the lesions is characteristic of sarcoid in a characteristic case, but a morphological diagnosis is dependent on clinical correlation and such a diagnosis is not justified on the basis of the discovery under the microscope of an isolated "sarcoid" lesion.

In a patient suspected to be suffering from sarcoidosis, a biopsy can be of great value in the confirmation or refutation of the diagnosis, and there must be few cases in which tissue cannot be obtained, whether it be a lymph node superficial or scalene, conjunctiva, tonsil or liver, spleen or lung recovered by an exploring needle.

Naked eye, the sarcoid material is often pale brown in colour, and under the microscope its characteristic feature is its monotony—a replacement of the normal tissue by congeries of epithelioid cells, uniform in size, with little tendency to coalesce, and though there may be a little fibrinoid in the centre of an epithelioid collection, there is never any caseation. The epithelioid collections are usually surrounded by a sharp margin of lymphocytes, and often there is hyalinization with a tendency to obliteration of the cellular elements and on occasions the development of the so-called para-amyloid; various types of inclusion bodies have been observed but are not of diagnostic significance.

It has already been emphasized that although the histological changes are characteristic in sarcoidosis, they are not diagnostic in isolation, and a very similar, if not indistinguishable, appearance may be found in solitary lymph nodes, draining areas of chronic tissue destruction; early tuberculous involvement in a lymph node or the tissue reaction in brucellosis, may simulate sarcoidosis and it is as well, whenever possible, to reserve a portion of the biopsy material for bacteriological examination. The giant cell granulomata, often affecting endocrine glands, which has been characterized so clearly by Rickards, is certainly distinct from sarcoidosis. If histology cannot of itself provide a definite diagnosis of sarcoidosis, are there any other laboratory procedures of greater value? Again the answer is no; there are hæmatological and biochemical changes to be observed in sarcoidosis, but they provide, at the best, supportive evidence.

Lastly, we must consider the value of the Kveim reaction, and although there has been contradictory claims with regard to this test, the majority of critical workers would feel that provided a satisfactory antigen is available—and this is the great difficulty—it is a valuable test, giving positive results in about 85% of cases acceptable as sarcoidosis on other criteria and less than 5% of false positives. Nelson's claim that positive results can be obtained

with normal spleen has not been substantiated, although it is true that sarcoid patients show a striking liability to form keloid scars after minor or major trauma and if these are examined histologically, they reveal the characters of the sarcoid granuloma. However, it is not sufficient to base the diagnosis of a positive Kveim reaction on the naked-eye reaction; there must be a biopsy of the lesion but this can usually be done with little inconvenience to the patient and often a punch biopsy is sufficient. Rogers and Haserick have made the intriguing observation that the injection of Kveim antigen and sarcoid serum into normal individuals will give a positive reaction.

The diagnosis of sarcoidosis in fatal cases is not difficult, if it is thought of, but it can seldom be achieved on naked-eye appearances and the usual cause of death is right heart failure consequent on pulmonary fibrosis or left ventricular failure due to severe involvement of the heart with sarcoid granulomata. When a case of sarcoidosis succumbs with tuberculosis, the sarcoidal and tubercular lesions remain distinct histologically, even though they may be present in the same organ.

When we come to the third question—the nature of sarcoidosis—it is well to start by collecting together the facts before considering hypotheses.

Sarcoidosis is a disease of temperate climates, affecting young adults of both sexes equally; cases have occasionally been described in twins or siblings but probably not frequently enough to suggest any genetic liability, and a recent suggestion that there was some linkage with the Rh blood group system has not been substantiated.

The incidence in the white races is a little under 1 per 100,000 population, but in the United States the disease is very much commoner in negroes than in white people in the same geographical area. Both in Scandinavia and the United States sarcoidosis occurs more frequently in rural areas than in towns.

The onset of the disease is usually insidious, but may begin with pyrexia or erythema nodosum, the extent and severity of the lesions gradually increase to a maximum and then regress with a duration of about ten years, although the residual visceral scarring with consequent dysfunction will persist. The incidence of tuberculous contacts corresponds to that seen in non-tuberculous normal controls.

Much interest has been shown in the immunological reactions in sarcoidosis and it can be said that there is no impaired ability to form antibodies; indeed the response to immunization may be exaggerated, nor is there any impairment to hypersensitivity reactions of the immediate type, but there is impairment to dermal sensitivity reaction of the delayed or tuberculin type, irrespective of the type of antigen used, and even when there is evidence, by complement-fixation tests of large amounts of circulating antibody. This phenomenon is not peculiar to sarcoidosis, but has also been observed in cases of Hodgkin's disease and other disorders of the lymphoreticular tissue and it may be related to the tuberculin neutralizing factor which Wells and Wylie detected in the globulin fraction of the serum in cases of sarcoidosis, leishmaniasis and lymphogranuloma inguinale—all disorders in which there is hyperglobulinæmia and a reactive proliferation of histiocytes or epithelioid cells. It may also be related to Pyke and Scadding's observation that the response to the Kveim reaction is inhibited by cortisone, but under cortisone therapy a positive tuberculin reaction may be obtained and this has also been observed by James and Pepys using "depot" tuberculin.

The results of the Middlebrook-Dubos hæmagglutination test for tuberculosis have not been entirely uniform in sarcoidosis, but the majority of observers have found negative results in about 80% of cases.

The response to therapy sometimes provides a clue as to the pathogenesis of a disease, but in sarcoidosis the findings are far from clear-cut; calciferol in a certain proportion of cases is beneficial, but in others it is definitely harmful, and this can be shown to be related to the hypercalcæmia which occurs in about 30% of cases and has been studied critically by Dent and his colleagues, although a satisfactory explanation for the association of sarcoidosis with this abnormality of calcium metabolism has yet to be propounded. Streptomycin and PAS have been claimed by some to be beneficial in the early stages of the disease but to have little or no effect in the later stages where cortisone may be effective, though the hazard of overt tuberculosis developing necessitates the simultaneous exhibition of PAS.

Lastly, although not strictly a form of therapy, sarcoidosis has been shown to be one of those curious diseases which are improved by pregnancy.

I think the factual evidence with regard to sarcoidosis would support the view that sarcoidosis is a disease state consequent on an immunological response to an unknown antigen and it is usual to characterize this response as an abnormal immune reaction, but this assumption may not be justified. In spite of a vast amount of experimental work, our understanding of the range of immunological response to antigens under varying environmental and nutritional

states is scanty in the extreme. There are a number of standard laboratory procedures which will induce characteristic acute reactions in experimental animals which are designated as an anaphylactic response, Shwartzman phenomenon, Arthus' phenomenon, tuberculin type allergic reactions, &c. Acute human disease counterparts to these laboratory models have been observed, but it seems to me quite unjustified to equate any of the acute reactions with the chronic immune reactions which are to be seen in many naturally-occurring diseases in man and animals associated either with infection and reinfection, as in rheumatic fever, or a state almost approaching parasitism as in chronic tuberculosis and leprosy.

Although there is a fair degree of agreement that the pathogenesis of sarcoidosis is a disturbance of the immune mechanism, there is no agreement as to the nature of antigen involved.

Naturally, the tubercle bacillus must first be considered, if only for historical reasons, and though it is at present in general disfavour as the ætiological agent, it is well to recall Schaumann's remark that "one is apt to reject the tuberculous theory when one *begins* to study the disease".

There can be no question that morphologically the lesions closely resemble those found in mycobacterial infections, and there is similarity in the organ distribution, with the exception of the cardiac lesions. The low incidence of tuberculous contacts and the inability to recover acid-fast bacilli from the established lesions, are used as evidence both for and against a tuberculous ætiology by the respective protagonists.

The lack of dermal sensitivity to tuberculin has ceased to be a useful debating point, since it has been shown that this "anergy" in sarcoidosis occurs with a wide range of antigens and is a feature of its pathogenesis rather than giving an indication as to ætiology.

There has also been dispute as to the significance of the development of tuberculosis in patients suffering from sarcoidosis. The majority of observers would agree that the incidence is high, but some would explain this by suggesting that the diagnosis has been at fault or that, not being tuberculous, they have been treated in sanatoria and so exposed to infection. The fact remains that when a sarcoid patient develops tuberculosis, the sarcoid lesions regress and they develop dermal sensitivity to tuberculin, although it should be noted that a considerable number of sarcoid patients in the spontaneous healing stage of the disease become Mantoux positive.

Those who support the tuberculous hypothesis would regard sarcoidosis as an example of tuberculous infection in which there is high resistance and immunity, but in which the immunological response has been associated with marked granulomatous reaction. They would suggest that there is a range of reaction of tuberculous infection, from the non-reactive "sepsis tuberculosa acutissima" of Scholtz to classical tuberculosis in its various forms and then to the hyperplastic tuberculosis of Ziegler, Gloyne's indolent tuberculosis and, finally, sarcoidosis. As a working hypothesis it is attractive but in reality the evidence in support of it is no better or worse than the evidence against it. It is of some interest that Zettergren compared with great care a series of cases of sarcoidosis and Ziegler's chronic hyperplastic tuberculosis and showed that their natural history was very different, yet he still supported the tuberculous ætiology.

There is no satisfactory evidence to support a fungal ætiology and though a viral ætiology has been put forward from time to time, the experimental claims have not been substantiated and nosologically sarcoidosis does not suggest a virus disease.

One has the hypothesis that the antigen is not microbic, but some foreign material on the analogy with Beryllosis and the localized silicotic granuloma or even that there is no specific antigen but that sarcoidosis is a primary proliferative disorder of reticular tissue characterized by epithelioid granulomata and that the biochemical and immunological abnormalities are due to the primary cellular dysfunction; this last hypothesis from a morphogenetic viewpoint seems most unlikely and though one would not deny the superficial similarity of the sarcoid and Beryllium granulomata, yet as diseases they are very different and the non-microbic antigen has remained as elusive as a microbic one.

I prefer to regard sarcoidosis as a disease characterized by a disturbance of the immune mechanism in relation to some mycobacterial antigen and that it would seem most likely that a clarification of its nature would be achieved if long-term immunological experiments were pursued on the lines adopted by Murphy and his colleagues in their studies of rheumatic fever.

I have attempted to present the problem of sarcoidosis from the pathological aspect avoiding as far as possible any bias and suggesting the problems to be resolved rather than presenting hypotheses to be destroyed.

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Section of Urology

President—DAVID BAND, F.R.C.S.Ed.

[*June* 21, 1956]

DISCUSSION ON URINARY INFECTIONS

Dr. W. A. Gillespie (Bristol Royal Infirmary): *Infection in Urological Patients*

I wish to describe some observations made by Mr. Ashton Miller, Mr. K. B. Linton and myself in a 28-bedded surgical ward in which there were 8 urological beds. Between April 1, 1955, and March 31, 1956, there were 107 urological patients; 84 had prostatectomies, 70 by the transurethral and 14 by the retropubic method. At operation, a plastic or latex catheter was left in for two to three days, to drain the bladder. The post-operative irrigation procedure varied. One surgeon used continuous irrigation with sterile saline flowing up a second narrow tube in the urethra, or through a catheter in the perineum. The other used intermittent wash-outs of sterile saline given with a bladder syringe up the indwelling catheter, as required, to remove clots.

Methods.—Urine was collected daily, with aseptic precautions, starting on the day before operation. The specimens were examined within one to two hours, by microscopy and by a roughly quantitative culture technique, using a standard loop. Patients whose urine contained at least 7,000 organisms per ml. on one occasion, or at least 2,000 per ml. repeatedly were counted as infected. These high limits were chosen deliberately, to exclude slight and doubtful infections.

Results.—Post-operative infections were very frequent. Of 64 patients whose urine before operation was sterile, all but 9 developed a post-operative infection, usually during the first three days (Table I). Many patients had mixed infections. Patients with urine infected before operation often acquired new organisms afterwards.

TABLE I.—POST-OPERATIVE INFECTIONS IN PATIENTS WHOSE URINE WAS STERILE BEFORE OPERATION

Number of patients	Escaped infection	Infected	Day of onset (after operation) 1	2	3	4	5	6	7	8
64	9	55	20	13	10	4	5	2	0	1

How severe were the infections? Judged from the urines, they were quite heavy, with several thousand bacteria per ml., and usually with many pus cells. On the other hand, clinical effects were usually slight or absent, although the infected patients had pyrexia more often that the others. Most of the patients suffered little harm, but a few infections did have serious consequences. This seemed particularly likely in heavy *Staph. aureus* infections, which occasionally caused pylonephritis and even septicæmia.

Most of the infections were acquired in hospital and were caused by endemic strains identified by their unusual resistance to antibiotics. In many hospitals, there has been a gradual accumulation of bacteria showing resistance to antibiotics to which they were previously sensitive. This has been caused by cross-infection and selection of resistant variants in a community in which the antibiotics are often used. The best-known example is the antibiotic-resistant "hospital staphylococcus", but the same thing has happened with others. Thus, coliform bacilli normally are sensitive to streptomycin and sulphonamide, but many strains isolated in this hospital are resistant (Table II); only 1 of the 31 patients with

TABLE II.—STREPTOMYCIN-RESISTANCE OF COLIFORM BACILLI CAUSING INFECTIONS OUTSIDE AND INSIDE HOSPITAL

Source	Total strains	Streptomycin Sensitive	Resistant
Outside hospital (infected on admission) ..	7	7	0
Inside hospital	40	9	31

a streptomycin-resistant coliform infection had had streptomycin. Clearly, most of the infections were caused by cross-infection in hospital, already so familiar in connexion with staphylococci.

Fig. 1 shows the organisms frequently isolated from urine after operation. The height

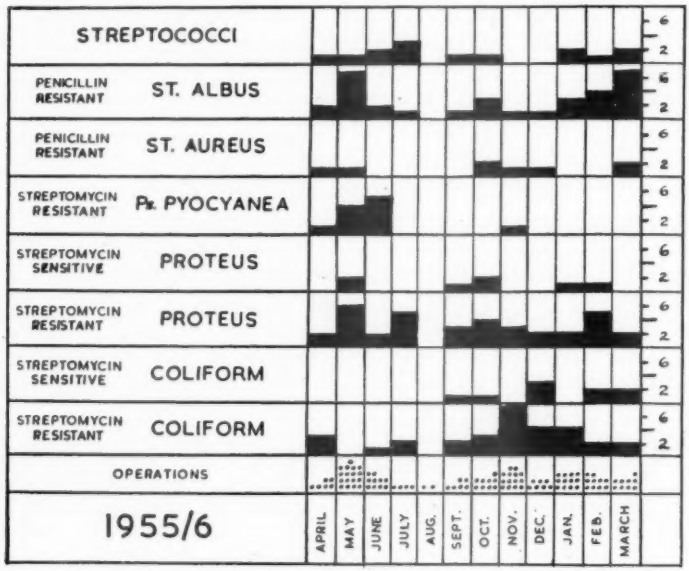

FIG. 1.—Organisms in urine after operation.

of each block represents the number of patients admitted during each month (except August) whose urines became infected with the organism. Many patients had more than one organism, successively or simultaneously. There was a run of streptomycin-resistant *Ps. pyocyanea* infections near the beginning, indicating cross-infection. Most of the proteus strains were streptomycin-resistant, whereas most pseudomonas and proteus strains acquired outside hospital were, like *E. coli* streptomycin-sensitive. All the *Staph. aureus* strains were penicillin-resistant, except for one not included in the figure.

We searched for similar organisms in the environment, using swabs and settle plates. In the theatre we found a very few Gram-negative bacilli on the floor but not elsewhere. We isolated them frequently from furniture, floor, blankets and urine-bottles in the ward. This did not prove that the ward was the more important source of infection, but it made it seem likely. Ward manipulations, such as bladder irrigation, are not usually performed with asepsis of theatre standard.

Organisms might have entered the urinary tract after operation in several ways. It was unlikely that in the time available they could have established themselves in a patient's bowel and gone from there to his bladder. We investigated this possibility by looking for streptomycin-resistant *E. coli* in the fæces of 56 patients. We failed to find them, although 14 of the patients had or subsequently developed urinary infections caused by these organisms.

The indwelling catheter was a likely channel of infection. In the first place, organisms might have travelled up outside it, in the urethral secretion resulting from mechanical irritation. To investigate this possibility we made daily cultures simultaneously from urethral meatus and urine, but found little connexion between organisms in the meatus and those found subsequently in the urine. Nevertheless, this mode of infection has not been excluded.

The inside of the catheter was a probable route. Organisms might reach it through the tubing connecting it to the non-sterile drainage receptacle at the bedside, perhaps aided by ascending air-bubbles. We did a controlled trial of the effect of using closed aseptic drainage (similar to that described by Pyrah *et al.*, 1955). In the patients who had no intermittent irrigation (but who had continuous irrigation), closed drainage often delayed the onset of infection, but did not prevent it (Table III). Moreover, the use of closed drainage

TABLE III.—INCIDENCE OF INFECTION WITH CLOSED AND OPEN DRAINAGE

Drainage	No. of patients	No. infected	Time of onset while catheter *in situ*	Time of onset subsequently
Closed ..	14	10	3	7
Open ..	48	36	27	9

reduced the number of different varieties of organisms appearing in the urine after operation (Table IV). Evidently organisms can ascend the drainage tube, but this is not the only route of infection.

TABLE IV.—EFFECT OF DRAINAGE ON INCIDENCE OF MIXED INFECTIONS

Drainage	No. of patients	No. who developed infections	No. of strains per patient 1	2	3	4	5
Closed ..	22	17	10	7	0	0	0
Open ..	83	62	20	19	17	4	2

Irrigation up the catheter by means of a sterile bladder syringe is very likely to cause infection. In a small group of patients who had retropubic prostatectomy performed by one surgeon, those with frequent bladder-syringe irrigation had a higher incidence of early post-operative infection than the others. The former may, of course, have been more susceptible to infection (Table V).

TABLE V.—IRRIGATION AND INFECTION AFTER RETROPUBIC PROSTATECTOMY

Frequency of irrigation	No. of patients	Post-operative infection while catheter in situ	Post-operative infection subsequently
Once a day	4	0	2
More than once a day ..	8	7	1

Clearly, infection can enter through the catheter. It can enter in other ways too; there were some infections in spite of closed drainage and no irrigation. Probably these patients are susceptible to infection by even a small number of bacteria. Unless special precautions are taken, more than this number are likely to enter the urinary tract, by more than one route.

I am very grateful to Mr. A. W. Adams and Mr. Ashton Miller for permission to work with their patients.

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Dr. William Goldie (Department of Pathology, St. James's Hospital, Leeds): *Urinary Infections and the Use of Antibiotics in Their Control*

Our interest in urinary infection largely started as a result of an investigation into the bactericidal properties of various antiseptics during an outbreak of *Ps. pyocyanea* infection which occurred in a small surgical ward of 17 beds in a Leeds Regional Hospital. This ward is devoted almost exclusively to the treatment of cases of prostatism, and almost all the bacteriological investigations described here have been carried out on patients in this ward.

The results and the measures taken to control the *Ps. pyocyanea* infection have been published recently (Pyrah *et al.*, 1955). Although our researches were carried out mainly with the *Ps. pyocyanea*, this was by no means the only organism responsible at that time for urinary infection. We used it, so to speak, as a "tracer" organism, and we measured the success of our efforts against urinary infection in general by their effect on the *Ps. pyocyanea*.

It soon became obvious from our *in vitro* tests that the bactericidal action of antiseptics against the *Ps. pyocyanea* was much poorer than against other organisms responsible for urinary infection, and that the presence of organic matter still further reduced their powers.

Among the antiseptics with the greatest effect on *Ps. pyocyanea* are domiphen bromide (Bradosol) and chlorhexidine diacetate (Hibitane) and we have used these in the few cases where bladder irrigation has been thought necessary. The results of bladder irrigation with antiseptics in established urinary infection have been uniformly disappointing and such treatment is now reserved for the few patients who require long-continued pre-operative bladder drainage. In such patients nightly bladder irrigation with a 1 : 2,000 solution of Bradosol or 1 : 2,500 Hibitane will usually, but not invariably, keep the urine sterile where no infection has been present at the start. It will not clear an established infection, and it is perhaps a measure of our opinion of the efficacy of bladder irrigation with antiseptics that in 1954 no patient was treated by this method.

Bladder Drainage.—When it became evident that we were getting nowhere with bladder irrigation it was decided to try out a closed bladder drainage system following prostatectomy. The method used has already been published (Pyrah *et al.*, 1955). It consists of a drainage bottle of 1 litre capacity which has a metal screw cap incorporating an inlet tube and an air outlet tube. A rubber drainage tube is attached to the inlet and the catheter is attached to the drainage tube by means of a Pyrex adaptor. Bottle, metal cap, drainage tube and Pyrex adaptor are sterilized by autoclaving. Immediately after catheterization either in the theatre or in the ward, and before the sterile towels are removed, the drainage tube is attached to the catheter and the bottle screwed into place. The drainage bottle is replaced by a fresh sterile one when it is full. Following prostatectomy, bladder drainage is continued until the urine is no longer blood-stained, that is to say, for from two to five days. Bladder irrigation is only practised where there is clot retention.

Drug Treatment.—If catheterization has to be performed before prostatectomy a sulphonamide drug is given and continued until the operation takes place. Following prostatectomy, streptomycin and penicillin are given for at least five days in those patients whose urine is sterile on admission; in patients with infected urine penicillin together with streptomycin or other appropriate antibiotics are given depending on the results of the sensitivity tests.

Urine Examination.—Specimens of urine are examined at the time of admission, before operation, on each of the first four post-operative days and before discharge. Mid-stream specimens are used throughout except when the drainage apparatus is being used; then the specimen is obtained by placing the screw cap of the apparatus over the open neck of a specimen bottle. Results are recorded as "sterile", "a few colonies", "moderate" or "heavy" growths. Organisms isolated from pre-operative specimens, and many from the pre-discharge specimens, are tested for sensitivities to a comprehensive range of antibiotics.

This routine treatment has now been in operation in this ward for over five years and we thought it time once again to assess our results and to find out whether the lower incidence of infection was being maintained. I have chosen quite arbitrarily the year 1954 for this survey. In the selection of cases, for which I also am entirely responsible, I have used only two criteria, (1) that the patient shall have been subjected to prostatectomy, and (2) that an adequate number of specimens of urine shall have been examined. All patients fulfilling these two criteria have been included. Of the 219 patients with prostatism admitted in 1954, 45 have had to be rejected on one count or the other and 174 patients remain for assessment.

Results.—Table I gives a summary of the incidence of urinary infection before and after operation.

TABLE I

Cases	Number		%
Total	174		100
Admitted with sterile urine	94		54
Admitted with infected urine	80		46
Discharged with sterile urine	64	84	48
Discharged with slight infection	20		
Discharged with moderate or heavy infection	90		52

TABLE II

Cases	Number		%
Total admitted with sterile urine	94		100
Discharged with sterile urine	49	56	60
Discharged with slight infection	7		
Discharged with moderate or heavy infection	38		40
Total admitted with infected urine	80		
Discharged with sterile urine	15	28	35
Discharged with slight infection	13		
Discharged with moderate or heavy infection	52		65

A surprisingly high proportion of patients (46%) were admitted with an infected urine and when this fact is taken into account it would appear not altogether unsatisfactory that nearly half the patients (48%) were discharged with a sterile or slightly infected urine.

In Table II a comparison is made between the incidence of urinary infection following prostatectomy in patients admitted with a sterile urine and those admitted with an infected urine. In the former group 56 out of 94 were discharged with a sterile urine as compared with 28 out of 80 in the latter group. 37 patients out of the 94 admitted with a sterile urine did not produce an infected specimen throughout their stay in hospital. Infection invariably followed bladder irrigation for clot retention.

TABLE III

Cases	T.U.R.			R.P.P.		
	No.		%	No.		%
Total admitted sterile	35		100	59		100
Discharged sterile	23	24	69	26	32	54
Discharged with slight infection	1			6		
Discharged with moderate or heavy infection	11		31	27		46
Total admitted infected	37		100	43		100
Discharged sterile	9	10	27	6	18	42
Discharged with slight infection	1			12		
Discharged with moderate or heavy infection	27		73	25		58

Table III deals with the two different types of operation, transurethral resection (T.U.R.) and retropubic prostatectomy (R.P.P.) and their infecting potentialities. The patients are again subdivided into those admitted with sterile and those with infected urine. Of the 72 T.U.R. patients, 34 were discharged with sterile urine or minimal infection, as compared with 50 of 102 R.P.P. patients.

On the other hand, if we consider those admitted with a sterile urine, the proportion discharged uninfected was considerably greater in the T.U.R. group than in the R.P.P. group (69% as compared with 54%). One might conclude from the figures given so far that it is easier by our methods to keep a urine sterile than to clear an infected one, and that a patient admitted for prostatectomy with a sterile urine stands a reasonable chance of being discharged uninfected.

TABLE IV.—CASES HAVING NO ANTIBIOTIC THERAPY

Cases	Admitted sterile	Admitted infected
Total	12	12
Discharged sterile	5	4
Discharged with slight infection ..	2	2
Discharged with heavy infection ..	5	6

A small group of patients received no antibiotics during their stay in hospital, and it is of interest that the incidence of infection is practically identical with that in patients who received antibiotics (Table IV).

TYPES OF ORGANISMS ISOLATED

The incidence of the more frequently isolated organisms is given in Table V. By far the most frequent was the *E. coli*, and it is noteworthy that *Ps. pyocyanea* was seldom encountered.

TABLE V.—BACTERIA ISOLATED

	All patients (Total 137)		Patients admitted "sterile" (Total 57)	
	Times isolated	No. of patients	Times isolated	No. of patients
E. coli	324	122	118	54
Staph. pyogenes ..	41	25	14	9
Ps. pyocyanea ..	18	10	3	2

Of the coliform bacilli isolated on first admission, approximately 60% were streptomycin-resistant. Our figures are incomplete for sensitivities of strains isolated from the pre-discharge specimens, but over 80% of the *E. coli* from these were streptomycin resistant.

LATE RESULTS

All patients who undergo prostatectomy are asked to report at the follow-up clinic three months after they leave the ward. For various reasons, it is not possible to have a specimen of urine from each patient examined bacteriologically. Of 57 patients where such an examination was possible, 31 had a sterile urine, and in a further 14 there was no pus and slight infection. 12 of the 57 had frank pyuria and a heavy infection. Many of the patients on whom bacteriological examination of urine was not done were reported to have "clear" urine, i.e. a specimen voided into a glass cylinder showed no haziness. It would appear likely that the incidence of residual bladder infection has fallen to a low level three months after operation.

DISCUSSION

The incidence of urinary infection in the period immediately following prostatectomy remains at about the same level as it did when closed bladder-drainage was first instituted six years ago; the incidence is certainly much lower than before the introduction of this method, but even in those admitted with a sterile urine an infection rate of 40% must be regarded as uncomfortably high. The *Ps. pyocyanea* is no longer a problem and the *E. coli* is the most frequently isolated organism.

The high proportion of streptomycin-resistant strains both of *E. coli* and *Staph. pyogenes* isolated in this ward is noteworthy and the continued use of streptomycin as a prophylactic would appear to be inadvisable. The number of resistant strains has greatly increased since 1950 and 1951 and it might be deduced from the stationary infection rate since that time that the antibiotic has played no part in preventing infection. This view receives some support from the small group of patients who received no antibiotic treatment and in whom the infection rate was no higher. One wonders whether, in fact, prophylactic antibiotic therapy should be practised at all and whether if it is persisted in the only result will be to breed more and more strains of bacteria resistant to more and more antibiotics.

Lastly there is the question of the origin of these infecting organisms. Our original investigations with *Ps. pyocyanea* led us to believe that the bacteria were introduced into the

bladder as a result of faulty techniques of wound dressing and catheterization. The isolation of so many streptomycin-resistant strains of *E. coli* and *Staph. aureus* from post-prostatectomy specimens is also suggestive that the organisms are introduced from without. While the bulk of the evidence goes to show that what happens is true cross-infection it may well be that in some instances infection may take place directly from rectum to prostatic bed. As a result of operative trauma new vascular channels must be opened up between rectum and prostate and the direct transference of organisms from one to the other would seem possible.

SUMMARY

(1) As a result of the introduction of a closed system of bladder drainage following prostatectomy the incidence of urinary infection in the immediate post-operative period has been nearly halved.

(2) Bladder irrigation during the post-prostatectomy period has been almost invariably followed by urinary infection.

(3) *E. coli* has been by far the most frequently isolated organism in these infections.

(4) A high proportion of streptomycin-resistant strains has been found.

REFERENCE

PYRAH, L. N., GOLDIE, W., PARSONS, F. M., and RAPER, F. P. (1955) *Lancet*, ii, 314.

Dr. K. F. Anderson (St. Paul's Hospital, London): *Recent Advances in the Chemotherapy of Urinary Infections*

Cases of urinary infection fall into three groups. In the first, a cure can usually be anticipated with any suitable agent, provided there is no previous history of infection or abnormality of the urinary tract. In the other groups, with a history of infection and abnormality of the genito-urinary tract, the prognosis is either moderate or frankly poor.

Chemotherapeutic substances should be chosen with due regard to nephro-toxicity and to efficiency in the face of impaired renal function. The emergence of resistant strains and reinfection with other organisms are two of the most serious problems encountered. *In vitro* sensitivity tests show a clear relationship to the outcome of treatment, but accurate assessment of sensitivity to the sulphonamides requires the use of media free from inhibitors.

Three new sulphonamides are available for the control of coliform infections. Sulphamethizole and sulphafurazole are structurally similar compounds with a low degree of acetylation and high urinary solubility. There is relatively little risk of crystalluria. Sulphasomidine shows even less acetylation and up to 90% remains in the free active form in blood and urine.

Triple sulphonamides seem to be less predictable in their action, and frequently the combination is less effective than the individual substances of which it is composed.

Experience with broad spectrum antibiotics has shown that while the acute, uncomplicated infections will respond with a high percentage of cures, those cases of long-standing infection will rapidly develop resistant variants. The toxicity of this group of substances, particularly upon the gastro-intestinal tract, is a further factor which makes their long-term use a matter for careful consideration. An important contribution to antibiotic therapy has been made by Stern, H., and Elek, S. D. (1955) *Brit. med. J.*, ii, 1304, who have demonstrated the value, *in vitro*, of combinations of substances for the suppression of resistant strains. Streptomycin and tetracycline, or streptomycin and chloramphenicol are the most effective, and either combination preserves the bactericidal property of streptomycin.

In the chemotherapy of genito-urinary tuberculosis, the prevention of the emergence of resistant variants is also accomplished, or delayed, by combined therapy. Whatever pairs of drugs are preferred, the outstanding features of successful treatment are the avoidance of the use of isoniazid alone, and the rotation of therapy using alternate pairs of substances. In general, two combinations are given for fourteen days and are alternated for at least six months.

A new chemotherapeutic substance, nitrofurantoin, exhibits some interesting properties. After oral administration, it appears in the urine in a state of stable supersaturation. Blood levels remain low, and general toxicity and the risk of crystalluria are negligible on normal dosage. The substance has a wide spectrum of activity and *in vitro* synergism has been demonstrated between nitrofurantoin, penicillin and streptomycin. The action on micro-organisms is essentially bactericidal and the agent is particularly effective in the control of infections with *E. coli* and Gram-positive cocci.

The following took part in the subsequent discussion:

The President, Mr. Wilfrid Adams, Dr. Cuthbert Dukes, Mr. Edgar Freshman, Mr. L. N. Pyrah, Mr. M. F. Nicholls, Mr. Hugh Donovan, Mr. E. W. Riches, Mr. A. C. Morson and **Mr. Marco Caine.**

The opening speakers replied to the discussion.

United Services Section

President—Sir LIONEL WHITBY, C.V.O., M.C., M.D., F.R.C.P.

[*June* 7, 1956]

Drowning

By Surgeon Commander J. W. L. CROSFILL, R.N.

THE physiology of the drowning process has been largely neglected academically and, I believe, the treatment of drowning has been for the most part dictated by custom, if not myth. The average practitioner sees little of drowning and can only rarely be called on for the immediate treatment. Usually it is the lay bystander who treats the semi-drowned. It is the riparian pathologist who sees most cases of drowning and it is only the forensic text-books which deal, *academically*, with drowning. Knowledge of what happens when a person is drowned is essential before rational treatment can be advised for the semi-drowned. This same knowledge is necessary before the pathologist can extend his research. Uncertainties and absence of information exist in both these fields.

I propose, therefore, to give a brief account of what happens in drowning. I am drawing my information from the published works of Swann and his associates in the United States who have worked on this theme during recent years.

If the man in the street were asked how people die by drowning he would say that they try to breathe under water, their lungs fill with water, they cannot get any air and so die. The doctor would probably say they are asphyxiated, which means the same thing. The same man in the street would say that artificial respiration must be given to the drowned and that it should be continued for two hours or more. He believes in *true resuscitation*, that is, the restarting of cardiac action with the re-establishment of spontaneous respiration, in an individual already *dead*. More informed opinion might say that recovery is possible if, although respiration has ceased, the heart is still beating. I am not sure that some medical men do not, unconsciously perhaps, subscribe to lay opinion and believe that prolonged artificial respiration might still be possible in a body, dead for some time after drowning. One must not, however, confound therapeutic enthusiasm with academic prognosis. In fact, academic assessment cannot be made until the physiological processes and the time factors involved in drowning are understood. The American studies were carried out on dogs, and this must be remembered when attempting to predict what might happen in man. Another point to be remembered is that the dogs were *totally* immersed—there was no struggling on the surface or coming up for the third or any other time. On immersion there is a period of breath-holding, followed by inspiratory movements during which water is taken into the lungs. Coma, with convulsive gasps, follows. Glottic spasm may or may not occur. Once water gains admittance to the alveoli, which present an enormous surface area through which osmotic interchange can take place, the course of events differs, depending on whether the drowning fluid is sea water or fresh water. By fresh water, I mean in this context, water free from electrolytes. When such fresh water enters the alveolar spaces it is very rapidly taken up by the pulmonary circulation, resulting in a gross local hæmodilution. At the same time local hæmolysis is caused and free hæmoglobin is present in the plasma. In sea-water drowning, a reverse osmotic flow takes place due to the higher saline content of sea water; thus water leaves the circulation and enters the alveolar spaces. There is then local hæmoconcentration in the pulmonary circulation, and hæmolysis does not now occur. These effects are indicated in Figs. 1 and 2. The animals were drowned by fitting a rubber hood over their heads, permitting blood sampling and other experimental procedures. Local anæsthesia only was used. Fig. 1, of fresh-water drowning, shows the development of hæmodilution in the blood from the left side of the heart, by the fall of blood density, hæmoglobin content and chloride concentration. The abrupt disappearance of pulse pressure is to be noted at 3½ minutes, which is about 1½ minutes after underwater breathing began, also that breathing movements continued after the pulse pressure had disappeared; that is, after effective cardiac output had ceased. Death in this animal occurred 6 minutes after immersion. Fig. 2 shows corresponding findings for a dog drowned in sea water. The appearance of hæmoconcentration is shown by the rising curves for the blood

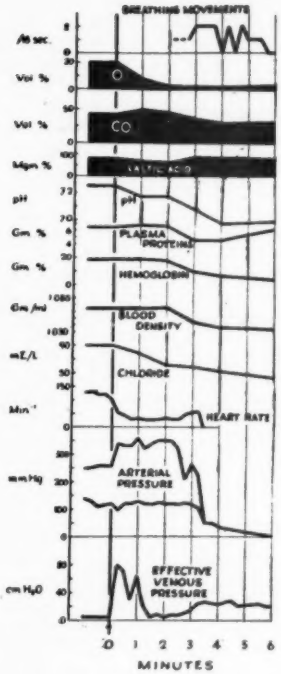

FIG. 1.—Course of fresh-water drowning. Dog No. IV.

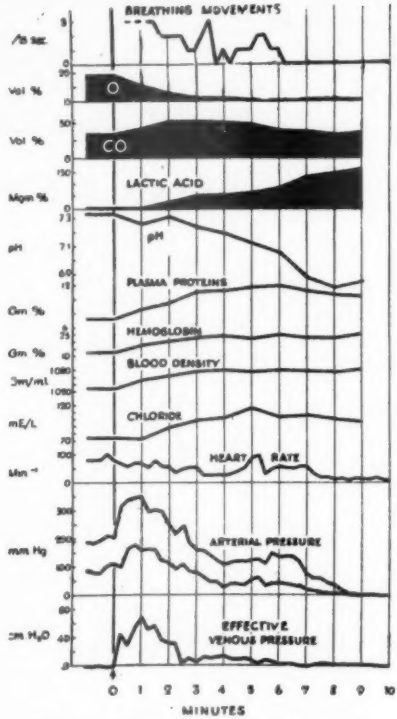

FIG. 2.—Course of sea-water drowning. Dog No. VI.

Figs. 1 and 2 are taken from Swann and Brucer, 1949: *Texas Rep. Biol. Med.*; by kind permission.

constituents and a rise in the density. There was only a brief period of breath-holding in this dog, apparently a minute or so less than in the previous slide. Respiratory efforts stopped after 6 minutes but a pulse pressure was still registered after 8 minutes. There is no abrupt disappearance of pulse pressure, the heart output as expressed by the systolic and diastolic pressure readings, gradually falls off and death occurs at 10 minutes.

Fig. 3 shows the differential effect of sea-water and fresh-water drowning on the blood density, but note that death tends to occur earlier in fresh-water drowning.

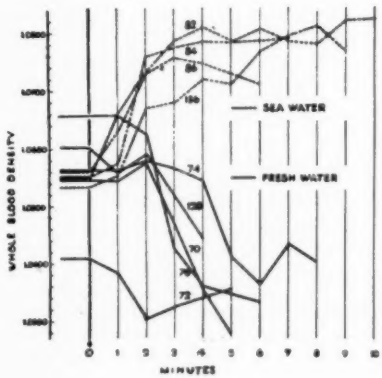

FIG. 3.—Blood density changes during drowning. (From: Medical Division Special Report No. 5. Conference on Artificial Respiration held at Medical Division, Army Clinical Center, Maryland, on September 29–30, 1950.)

Using deutarium oxide as a tracer, given intravenously before the experiment, it was shown that in fresh-water drowning circulatory fluid also appeared in the alveoli, together with chloride and protein—indicative of a pulmonary œdema. Similarly in sea-water drowning magnesium appeared in the blood returning to the heart and *again* there was a terminal pulmonary œdema. Death occurs before the alveolar fluid contents reach osmotic equilibrium with the pulmonary circulation. It is the presence of this plasma protein in the alveolar spaces that causes the typical fine, persistent froth seen in the airways of the drowned.

The abrupt fall in pulse pressure and the earlier death in dogs drowned in fresh water was due to the onset of ventricular fibrillation, which did not occur in dogs drowned in sea water. Ventricular fibrillation in fresh-water drowning is believed to be due to the dramatic and gross fall in the sodium concentration in the blood reaching the left heart. This local hæmodilution may cause a reduction to half or more of the original concentration. The potassium-ion concentration does not fall *pari passu* with the sodium. As a result of hæmolysis and the consequent liberation of potassium into the plasma as well as the increase in plasma potassium which occurs solely as a result of anoxia, the potassium concentration is less reduced than that of sodium. It is thought that this disturbance of the potassium-sodium ratio, in favour of potassium, is an additional factor in the production of ventricular fibrillation. The less fresh water inhaled, the less the risk of fibrillation (ventricular) and the greater the chances of resuscitation. But since the fresh water passes with great rapidity into the circulation, when large amounts are inhaled the lethal damage may be done within the first minute or so of submergence.

Some dogs showed evidence of considerable hæmodilution but had dry lungs when examined post mortem. The general tendency, however, was for residual fluid to be present in the lungs, somewhat more in the case of sea-water drowning. The osmotic effects were explosive in appearance, being demonstrable within seconds of inhalation of water.

So much for the biochemical background in drowning. It remains to be answered:

(i) At what point in the events leading to death may these processes be reversed and what are the time relationships involved?

(ii) At what point does irreversible cerebral damage occur as a result of anoxia?

The Americans extended these studies to examine these problems both in drowning and in other forms of death from anoxia.

The experimental method was to attempt resuscitation, by insufflating the animal's lung with oxygen, at various times during the terminal decline of the blood pressure. Fig. 4 gives the findings in fulminating anoxia occasioned by breathing pure nitrogen. Similar work was done in sea-water drowning but the full results are not yet available to me and the data are not yet complete, but provisional findings will be given. Drowning in fresh water

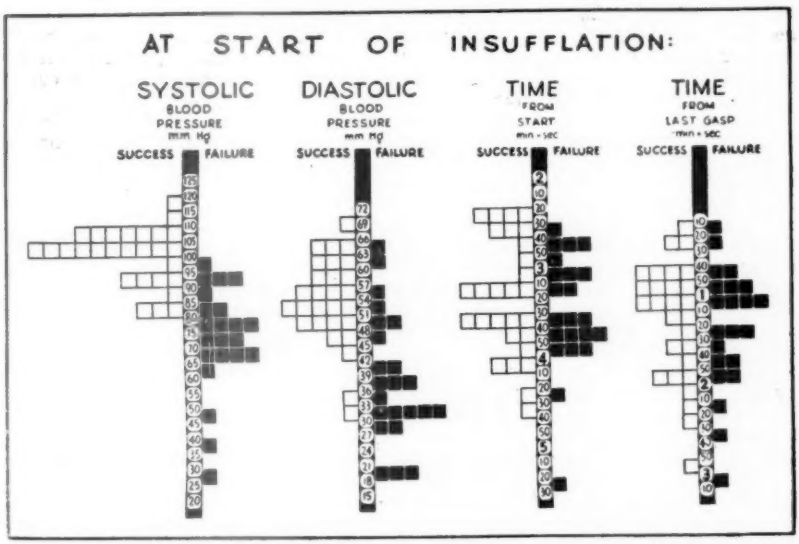

FIG. 4.—Use of various criteria to determine the imminence of circulatory failure in fulminating anoxia. (From: Swann and Brucer, 1951: *Texas Rep. Biol. Med.;* by kind permission.

cannot be examined by this technique, due to the onset of ventricular fibrillation. The open squares represent successful resuscitations, the black squares failures to resuscitate. It is readily appreciated that all animals whose systolic pressure was above 100 mm. of mercury were revived. When their systolic pressures were between 80 and 100 some revived and some died. When the systolic pressure fell below 80 there were no successes. No such clear-cut points of success and points of failure are apparent when the diastolic pressures are considered. Similarly there appears to be no obvious success and failure indication when the time elapsing between the beginning of the anoxia and the institution of insufflation, or to the time between the last gasp and the insufflation are considered. The level of the systolic pressure at the time when artificial respiration is given appears to be the significant factor determining whether or not the animal will survive.

The results of this experiment carried out on 13 dogs only, drowned in sea water, indicate that the point of success is 115 mm.Hg, and 50 mm. the point of failure. The point of failure is given with reservation by the experimenter (Dr. H. G. Swann) as an estimate only. The *time* taken for the systolic pressure to fall from the point of success to the point of failure is all-important. This is only 16 seconds in Fig. 4 which is for fulminating anoxia due to pure nitrogen inhalation. The figure, given as an estimate only for the 13 dogs drowned in sea water, is 20 seconds. Thus it is clear that, once the systolic pressure falls to the critical level there is only a fraction of time available in which successful resuscitation might be carried out, a time to be reckoned in seconds rather than minutes. What one would like to know is how long may a human being be immersed before he reaches this critical point of success. I have no information on which to form any estimate but some idea of the length of time man may remain totally immersed before death occurs can be formed. It was found that the hearts of *all dogs* had stopped beating after 11 minutes, regardless of the type of drowning. Even in simple obstructive asphyxia in dogs, unaccompanied by any aspiration of fluid, which might hasten death, circulation fails in all dogs by the twelfth minute. Complete submergence therefore would be invariably fatal in dogs by the twelfth minute. Swann records that there is some evidence which suggests that *man's* heart may be able to tolerate slightly longer periods of asphyxia-anoxia than dogs. Heart sounds and sphygmographic records have persisted for as long as 14½ minutes after death from hanging. As the physiological events in failure to oxygenate are similar in death from hanging and drowning, it may be presumed that the maximum time it is possible for the heart's action to continue in total immersion is of the order of a quarter of an hour. Allowing five minutes as a margin of error Swann considers 20 minutes' complete immersion as the *maximum* time for man's heart action to continue. The osmotic events can only be supposed to reduce this time. In practice it is fairly certain that the actual time is much shorter where the victim has aspirated fresh water and more than probable that it is also less in salt water drowning. This time limit of 15–20 mins., refers, of course, to cessation of heart action, it does not mean that resuscitation is possible after this length of time. In fresh-water drowning the biochemical changes are explosive in character, and the ventricular fibrillation once initiated is irreversible. Swann believes that in man death may occur after 3 minutes submergence in fresh water and that he is usually dead within 8 minutes.

In obstructive asphyxia an overwhelming cerebral insult is done to dogs by the tenth minute. Man's brain is said to be even more susceptible to anoxia than the dog's brain, so that, although the heart may still be beating after that time, it is extremely unlikely that man would be able to be resuscitated *and survive*, after 10 minutes of total immersion, or even less.

One is forced to the conclusion, therefore, if the experimental evidence quoted and the inference drawn from it are valid, that man may be immersed and die within a few minutes in fresh water if ventricular fibrillation supervenes, but may survive somewhat longer in sea water, but is in either case likely to die before the onset of irrecoverable cerebral damage. On the other hand it is *theoretically* possible that he might still be alive, in the sense of continuing cardiac action and yet be suffering from the various paralyses of cerebral damage due to anoxia. Post-submergence anoxia—dementia paralytica—however, is a theoretical syndrome of which I have never heard in man. In view of the large number of people who are *claimed* to have been saved by artificial respiration after prolonged immersion it is surprising that no such syndrome exists. It ought to exist. That it does not suggests to me that those who are saved by artificial respiration are those whose systolic pressure has not fallen below the critical level—whatever that might be for man—and in that this critical time must be at or less than the time needed for cerebral insults to appear. It seems fair to conclude that, in round figures, 10 minutes' total immersion for man is the *maximum* at which one *can* obtain recovery. Even this extreme limit falls far short of traditional stories.

The practical implications of these experiments and inferences are clear. No time should ever be wasted in attempting to *examine* a semi-drowned individual. The point of success of the systolic pressure may be near at hand; if so, there are only a few seconds available in which recovery may or may not be possible. After those few seconds no recovery is possible.

Immediate artificial respiration is called for—in my opinion no attempt should be made at clearing the mouth, removing false teeth or similar manœuvres. In fact a medical bystander might be a danger to the victim if he yields to his clinical instincts and attempts to feel the pulse or make any other examination, thereby delaying artificial respiration. I would even go farther and suggest that life-saving teaching should include instructions that attempts at artificial respiration should be made whilst the rescuer and the victim are still in the water. This is by no means impossible, especially in the case of children.

I should now like to turn to one or two aspects of drowning which present problems to the pathologist. The classical appearances of drowning are cyanosis, fine persistent froth in the airways, ballooning of the lungs, a dilated right ventricle filled with dark, fluid blood, and drowning fluid in the lungs and stomach. Foreign bodies, be they weeds, mud or diatoms, may be found in the airways and lungs.

In the majority of cases some or all of these findings are present, and post-mortem diagnosis is then simple. Occasionally, however, froth and fluid in the lungs are absent and ballooning is by no means a constant finding. When putrefactive changes are present, a not infrequent state of affairs, the findings at post-mortem are often indeterminate and the diagnosis of "asphyxia from drowning" may not then be founded on much more than assumption. The osmotic exchanges which take place in the pulmonary circulation offer a theoretical means of determining whether drowning has occurred. Gettler carried out investigation as long ago as 1921 in which he compared the sodium chloride content of the blood in the left side of the heart with that on the right. He found that in fresh-water drowning there was diminution in the chloride concentration in the left heart relative to the right heart blood and the reverse in the case of salt-water drowning. His controls showed no appreciable differences. On the face of it, here is a simple procedure to assist the forensic pathologist. Unfortunately there are difficulties. It is often found that the blood in the left heart is clotted and sampling is thereby invalidated. Technical difficulties apart, the points which remain to be determined are, firstly, how consistent are the findings and secondly, how are the results affected by the lapse of time after death. Moritz (1944), in America, has shown that in animals, although there may be concentration difference between the blood in the two sides of the heart, yet, with lapse of time there is a fall in concentration of chlorides which does not proceed at the same rate in the two ventricles, so that, after a lapse of time, the two readings tend to equal each other. He considers that any observed differences are not of evidential value when the blood is obtained more than a few hours after death. I have been able to carry out a few pilot experiments of this nature on humans. A typical result is that of an athletic man (age 37) drowned in the Thames whilst coxing a racing eight. His body was recovered within minutes—incidentally this was an example of a very quick death in fresh water—and his heart blood was obtained twenty-three hours later, the body having been kept in the mortuary refrigerator in the meanwhile. The average for four blood samples from the right ventricle was 505 mg.% of sodium chloride (range 494 to 517) and 451 mg.% NaCl in the left ventricle (range 447 mg. to 456 mg.). In this case there was a difference of 54 mg.% between the two sides. This is possibly a valid example of left-sided hæmodilution. Another case, that of an elderly man immersed in fresh water for an estimated forty-eight hours and kept for a further twenty-four hours in the refrigerator gave the following results: 307, 307, 304 mg.% NaCl in the right ventricle and 278, 298, 298 mg.% NaCl in the left ventricle—the average difference being 11 mg.%. The smallness of this difference and the low chloride concentration in the right ventricle believed to be due to post-mortem decrement made this result of no significance in determining the presence or otherwise of hæmodilution due to drowning. It is hoped that as more data become available, the consistency and reliability of this test may be assessed, and that the significance of the findings in relation to time after death may be determined. Not only the chloride but other ion concentrations, the specific gravity, the cell count and other biophysical approaches are possible means of determining the presence of hæmodilution or hæmoconcentration. At present the difficulty is that of obtaining a valid sample of blood from the left heart.

The forensic pathologist is interested in the presence of foreign bodies in the alveoli. It has been held that, although foreign bodies might make their way into the trachea or larger airways after death, their presence in the alveoli must necessarily indicate that the body was alive and respired whilst in the water. Such an inference might on occasion have grave legal implications. To me this inference appeared suspect and I was fortunate in being able to carry out some experiments in conjunction with Dr. F. A. Holden of the Home Office in which we were able to demonstrate the presence of diatom fragments in the lungs of rabbits already dead, whose bodies had been immersed for a week in a tank filled with diatomaceous water (Fig. 5). The rabbits were handled extremely gently to avoid milking the diatomaceous fluid into the lungs but this could not be absolutely avoided and in fact critical attempts to avoid it were not made. Any human cadaver placed in water, to conceal

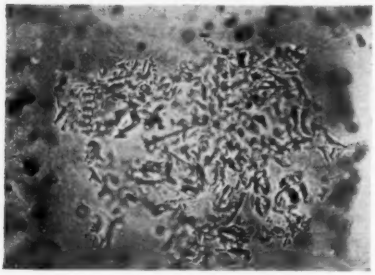

FIG. 5.—Diatomic fragments in lung of a rabbit immersed, after death, in a diatomaceous water and left therein for a week.

crime for example, is subject to movement due to currents and handling when recovered from the water, if not to actual attempted artificial respiration, and is undoubtedly subjected to a milking process. I consider it is demonstrated that under these circumstances it is possible for particles of the size of the diatomic fragments we used (20–25μ) to make their way into the alveoli. Thus the mere presence of a foreign body in the lung does not *necessarily* indicate that it must have got there as the result of any inhalation—in other words the victim was not *necessarily* alive when he entered the water.

Of the many interesting points there are two which I should like to mention. The appearance of a massive hydrothorax which is seen in those bodies recovered after several days. This hydrothorax fluid may be deeply blood-stained. One would like to know how long it takes for such to develop, whether the temperature of the water affects the rate of its formation, whether the blood-staining is a late phenomenon or whether it may be present *ab initio* and lastly, are the time intervals and eventual volumes different according to whether the drowning medium was fresh or salt water. One would assume, for the osmotic reasons previously mentioned, that there is more chance of a lung containing large amounts of fluid at death in the case of sea-water than in fresh-water drowning, and it is to be expected that more water would then be found in the thorax. Presumably the fluid is a post-mortem transudate.

Traditionally the drowning man clutches at straws. The textbooks state more specifically that objects may be found grasped in the hands of victims and may serve to indicate where the victim entered the water. Perhaps the classical example occurred in the famous Brides in the Bath case. One of these brides was found to be still holding a piece of soap in her hand. The point that puzzles me is by what physiological mechanisms is it possible for objects to be retained firmly in the hand after death by drowning. Cadaveric spasm is a curious physiopathological problem. It is said to occur in cases of violent, sudden and emotional death such as is present in suicidal cut throats. These people are occasionally, but not always, found to have the razor grasped tightly in the hand. What can be conveniently but probably inaccurately described as a grasp reflex must be present at and persist after death. Its causation is unknown. It must not be confused with rigor mortis.

The bride in question undoubtedly died of drowning, so much was apparent in the evidence given at the trial. I do not know how valid the inference is, but I suggest that death in her case must have come with explosive suddenness. Otherwise I cannot understand, if she died in a terminal coma, how she managed to retain the soap in her hand. Unfortunately I was not able to obtain the original post-mortem notes for a detailed account of the pathological findings. One would like to know how tight the grasp of the soap was. I myself have never seen this persisting grasp in drowned cadavers but once saw one body recovered from the cabin of a rammed and sunken ship. This man, recovered some days later, was found to be still grasping a gold watch in his hand. Unfortunately this had been removed by the time I saw the body. I was told of one body which was found grasping the bars of an underwater grid from which the body was only released with some difficulty.

If it is true that cadaveric spasm occurs in drowning and if it is also correct that death must necessarily be rapid in these cases, then I suggest that here is a pointer to another problem to which no answer is known to me, namely "Is it possible for sudden death to occur on immersion as a result of vagal stimulation?" Is there a risk of sudden death from cardiac arrest when jumping into water? If so, how frequently does it occur? The answers are not merely academic. They have a very real practical bearing in wartime, when so many men have to jump into the cold sea. If it is correct that very rapid death from ventricular fibrillation may occur in fresh-water drowning the cadaveric spasm is quite feasibly present. However, since fibrillation death does not occur in salt-water drowning (at least in dogs) then death is presumably longer drawn out and preceded by a period of coma. Under these circumstances cadaveric spasm is presumably less likely. On the other

hand, if death from vagal stimulation is at all present it might be expected that such bodies, in sea water, would on occasion present cadaveric spasm.

Two circumstances have been mentioned in which it is possible that no fluid would be found in the lungs of people presumptively "drowned". They are those cases in which explosive death occurred consequent on hæmodilution with more or less complete absorption of the fresh water and without appreciable reverse flow into the alveoli due to pulmonary œdema, and those cases in which death was due to vagal stimulation. There is, however, another possibility. Inhalation of the drowning medium may cause spasm of the glottis which, if persisting, could, in theory, lead to death from obstructive asphyxia alone. Whether or not this happens in fact I am unable to say. In deaths of these types, where dry lungs are found, it is possible that chemico-physical analysis of the right and left heart blood might be of assistance.

There are two other aspects to be considered. I have previously suggested that, were it possible to resuscitate individuals who had been immersed for longer periods of total immersion than 10–15 minutes then we ought to hear of cases of "anoxic dementia paralytica". But I wonder if there ought not to be another clinical entity—post-immersion emphysema. Fig. 6 demonstrates the histology of drowning; note the gross typical destruction of the alveolar architecture.

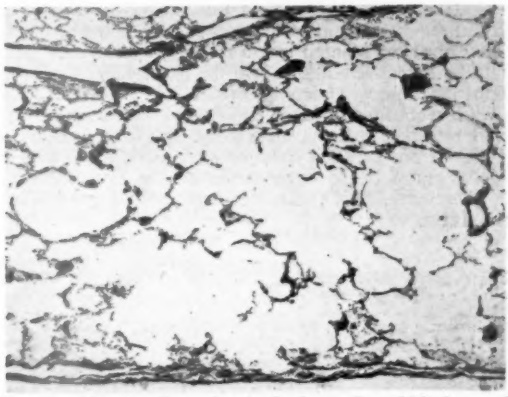

FIG. 6.—Alveolar disruption in the lung of a rabbit drowned in sea water.

I cannot conceive how any animal or man could survive such lung damage without suffering considerable disability from emphysema afterwards. I am presuming that such alveolar damage must take place in all those cases of semi-drowning who have inhaled water and whose respiratory efforts have churned up the protein in the pulmonary œdema fluid into the typical fine froth. Whether or not this is the correct mechanical causation of the alveolar damage I do not know. Perhaps over-distension by the entering water may play a part. Whatever the means, it is to be supposed that some destruction of the alveoli of this nature if not degree must occur in those individuals who are alleged to have been taken from the water unconscious. And yet should this not be a well-recognized clinical entity since so many hundreds of individuals are supposedly rescued and resuscitated every year? Should not dyspnœa be present even immediately after recovery? I have never read of it in the reports I have scrutinized. Of the few cases of which I have detail, those sent to hospital seem to require no prolonged stay. I am beginning to wonder more and more what is the actual physical condition of people who, it is claimed, are resuscitated from near-drowning. Have they really inhaled significant amounts of water, are they merely suffering pure obstructive asphyxia and spasm of the glottis? We know a certain amount about those who die but little about those who are revived.

It is surprising how little after effects are apparently felt by those who have been thought to be nearly drowned. I have had the privilege of reading many official accounts of incidents where, rightly or wrongly, artificial respiration was applied to the victims and yet they recovered quickly and were able to go home. Most of the records I have seen give insufficient clinical detail for any critical assessment to be made but I will quote two cases in which I was able to interview the rescuers. The first was that of a man recovered from the Thames by

the police. The man was apparently unconscious and cyanosed and was stated to have recovered consciousness after artificial respiration had been applied for about a quarter of an hour. This man was sent to a neighbouring hospital forthwith, where an X-ray of the chest was taken that same day. Unfortunately the intervals of time could not be ascertained. There were no clinical signs of abnormality and the X-ray was reported as being normal. Yet this man was alleged to have been unconscious from immersion only a few hours previously. I was able to see the films of another case who was found lying on the bottom of the deep end of an open-air swimming pool. Here again artificial respiration was given for about a quarter of an hour after which the man recovered consciousness. He was seen as an out-patient at a neighbouring hospital, about an hour after the incident and was X-rayed then and there. The X-ray appearances were those of normality and no abnormal clinical signs were found except for emotional disturbance and an associated tachycardia believed due to the man attempting to hide the fact that he was an epileptic. He appeared none the worse for his experience. It would be interesting to know if a similar absence of radiological findings is present in the case of sea-water incidents.

Finally, I would like to conclude with a few observations on the treatment of the semi-drowned. I believe that there is one and one only recommendation to be made and that is *immediate* artificial respiration. Never attempt a clinical examination, never try to clear the mouth, drain fluid from the airways or indeed bother about anything other than efficient artificial respiration for the first fifteen minutes. I believe that if you are going to be successful you will succeed in much less time than this, however. Theory suggests that once oxygenation is restored the myocardium will recover and, if the respiratory centre is viable, it will recover quickly once oxygenated blood is being circulated. Once the patient takes a spontaneous breath he is recovered, although the possibility of relapse should be remembered. This does not mean he will become conscious. This latter may be delayed and so may account for alleged recovery from semi-drowning after long periods of artificial respiration. To the layman, return of consciousness is the criterion of recovery but from our more academic point of view I am satisfied that we have done all that is necessary or indeed possible once we have restored the oxygenation of the myocardium and recovered the respiratory centre. The treatment is a matter of urgency and speed of institution of artificial respiration is all-important.

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BOOK REVIEWS

The Cervical Syndrome. By Ruth Jackson, B.A., M.D., F.A.C.S. (Pp. viii + 130; illustrated. 34s.) Oxford: Blackwell Scientific Publications. Springfield, Ill.: Charles C. Thomas. 1956.

The author defines the cervical syndrome as "a group of symptoms and clinical findings which occur as a result of irritation or compression of cervical nerve roots in or about the intervertebral foramina". The inclusion of cases of peri-arthritis of the shoulder and sprain of the extensor origin at the lateral epicondyle of the humerus, conditions not primarily due to such irritation, expands her conception of the syndrome, and the suggestion that by a mechanism not elucidated the cervical root irritation results in reflex stimulation of the cervical sympathetic system extends it still further so that such symptoms as ocular pain, blurring of vision, and vertigo are considered to be a part of it.

The lesions considered to be responsible for cervical root irritation are discussed. Subluxation of cervical vertebræ, osteophytes in intervertebral foramina, and fractures are considered important, as also are swelling of sprained capsular ligaments, of dural nerve sheaths and of the nerves themselves as well as adhesions secondary to such changes. It is even thought that posterior displacement of the vertebral artery in hyperextension of the neck may compress the cervical nerves. Trauma is considered important in the production of these lesions but abnormal laxity of ligaments, postural abnormalities and degenerative joint disease may be responsible; other suggested causes are inflammatory lesions such as "toxic capsulitis" and emotional stress. Arguments are put forward to show that cervical disc protrusions occur rarely and that they cannot give rise to nerve root irritation without producing evidence of compression of the spinal cord.

The difficulties of diagnosis are revealed in the report of 4 fatal cases treated as examples of the cervical syndrome, two of whom subsequently proved to have bronchial carcinomata, one a cerebellar tumour, and the last a coronary thrombosis and duodenal ulcer.

Treatment takes the form of local heat, massage, local anæsthetic infiltrations, traction, attention to posture, immobilization and psychotherapy. No mention of therapeutic exercises is made.

Although the author's painstaking approach has certainly been helpful to her patients the conception of the cervical syndrome is unlikely to prove a useful one. Its symptomatology is too diffuse, its objective signs too vague and for the most part its pathology is hypothetical—the lesion which has been proved to be responsible for many cases of cervical and brachial pain, a disc protrusion, is dismissed as an anatomical impossibility. However, since the great majority of cervical disc protrusions heal spontaneously and do not require surgical treatment the views expressed in this monograph will be beneficial in encouraging a conservative attitude, even though for the wrong reason.

Breast Feeding. By F. Charlotte Naish, M.A., M.D.Cantab. 2nd edition. (Pp. xiv + 161; illustrated. 12s. 6d.) London: Lloyd-Luke (Medical Books) Ltd. 1956.

This is a book clearly written, well printed and of a convenient size and price to allow it to be widely read by expectant mothers and their professional advisers.

Dr. Naish has the advantage of a very practical approach to her subject both as a mother and general practitioner. The preparatory chapters on "The Mind of the Mother" and the "Physiology of Lactation" give a sound basis for the reader to consider problems of lactation.

The following chapters are arranged in weeks. In each week a plan for feeding is given and the minor complications which may arise in mother and child; this is a good arrangement especially for the guidance of mothers.

Professional readers will naturally not always agree with all details of treatment, but the book is one which can be highly recommended to all readers.

Modern Cosmeticology, Vol. 1. By Ralph G. Harry, F.R.I.C. 4th edition. (Pp. xxxiv + 786; illustrated. 65s.) London: Leonard Hill (Books) Limited. 1955.

This is the first volume of a text on the principles and practice of modern cosmetics, dealing with their preparation and uses, to which both the dermatologist and chemist can refer. Details of the materials used in cosmetics may be found in the second volume. That this is the fourth edition in fifteen years indicates that there is a need for such a compilation. The subject is dealt with in very great detail from the dermatological and chemical and pharmaceutical aspects to their mutual advantage. Not only have we a series of receipts for British and American cosmetics but also a series of discussions of the basic principles underlying their composition and manufacture. We thus have a collection of

useful, sometimes curious information gleaned from widely scattered fields, usefully salted with the author's criticisms. The author is fully alive to the potential dangers that may sometimes arise from the use of such preparations and is very careful to point out early enough where medical advice or supervision may be needed. Throughout he has dealt with the various difficulties in a responsible manner and where matters are still under dispute he gives a balanced summary of the arguments. A book of this nature, addressed to widely differing disciplines, has its intrinsic difficulties of selection and degree of detail but they have been largely overcome. The dermatologist will find how substances penetrate or affect the skin and its appendages and how to use this information for his own purposes more efficiently and the chemist should be better able to understand what is required of him and the limitations within which he must work. The importance of physical chemistry is obvious throughout the work and the curious will be surprised at the complex background of such preparations as creams, lotions, suntan preparations, lipsticks, hair dyes and hair waving preparations and barrier creams, &c. Now that cosmetics are accepted so widely it is gratifying to find the subject dealt with so thoroughly and critically; this book should do much to assist in the proper assessment of their capabilities. The author's work has been worth while.

Clinical Electrocardiography, the Arrhythmias. By Louis N. Katz, A.B., M.A., M.D., F.A.C.P., and Alfred Pick, M.D. (Pp. xiii + 737; 415 illustrations. £6 10s. 0d.) London: Henry Kimpton. 1956.

The field of electrocardiography has widened so much during the past decade that the authors have found it necessary to divide the subject into two parts; the present book deals with arrhythmia, and a second is to describe electrocardiographic contour.

It is not unnatural for a treatise on arrhythmia to show a number of bipolar lead electrocardiograms without the addition of chest leads because they usually suffice; even the rather obsolete CF lead is not out of place, but there is mention in the text that auricular activity is best displayed by the right pectoral cardiogram and in CR rather than V leads. It is natural, too, that a surfeit of tracings should be exhibited, but the detailed legends appended to the individual cardiograms in this book are usually tedious and often redundant, for the kind of rhythm is clearly portrayed in the tracing although the exact mechanism of the events in the cardiac cycle demands precise interpretation. The illustrations themselves, numerically prodigious, are usually of a high order except that the wide fibre which records so many of them frustrates a clear display of auricular movement should this coincide with ventricular contraction, while the punched identification marks on the cardiogram rob it of an artistic presentation.

This is a ponderous and exhaustive treatise on all aspects of cardiac arrhythmia, but when the curriculum of the medical student is expanding so rapidly, and when he is expected to know about the diagnosis and the treatment of every form of arrhythmia dealt with in this book, it should be the aim of teachers to curtail rather than to expand a description of the knowledge they intend to impart, and bring it to the student in a convenient and inexpensive form. This book of 737 pages and 415 illustrations, and priced at £6 10s., does not fulfil this practical requirement, so that it can only find a place in the library of the physician whose main interest lies with cardiology.

Life of Sir John Bland-Sutton. By W. R. Bett, M.R.C.S. (Pp. viii + 100; illustrated. 20s.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

The Presidents of the Royal Society of Medicine and of its predecessor the Medico-Chirurgical Society have always been distinguished and often outstandingly brilliant men. It is surprising therefore that on looking through the list we find so few who have been the subject of a published biography. During the past eighty years only two surgeons have been so honoured—Sir James Paget and Sir John Bland-Sutton. Stephen Paget enshrined his father in his affectionate and delicate prose. In this recently published book Dr. Bett has painted a vivid and attractive picture, true to life, of Sir John Bland-Sutton. In both of these instances autobiographical notes by the subject of the biography helped considerably to produce the full effect.

Dr. Bett has different sections dealing with the various aspects of the character of the great surgeon he depicts; he succeeds in conveying to the reader a good idea of the difficulties, struggles, and successful achievements of one who had nothing but his own natural ability and untiring application to depend upon in his progress from the bottom to the top of the surgical tree.

Dr. Bett knows well the value of the well-turned phrase, and it is not out of keeping that he has dedicated this book to another doctor and famous writer—Dr. Somerset Maugham. There are some very fine photographs of Sir John accompanying the text.

Man in a Cold Environment: Physiological and Pathological Effects of Exposure to Low Temperatures. By Alan C. Burton, Ph.D., and Otto G. Edholm, M.B., B.S. (Pp. xiv + 273; illustrated. 30s.) London: Edward Arnold (Publishers) Ltd. 1955.

This monograph was originally commissioned by the Defence Research Board of Canada presumably with the object of providing those concerned with the care and protection of military personnel with a convenient compendium on the effects and dangers of a cold environment. The monograph, of course, goes much farther than this and will appeal to a wider public.

It is concerned with the relationship of homeotherms, and in particular man, to the laws of thermodynamics. The declared aim of the authors is the presentation of a unified and consistent scheme for the evaluation of the problems of man in a cold enviroment. To this end Burton and Edholm and other workers in this field have created what is practically a new subdivision of biology in that it has a jargon peculiar to itself, a courageous if as yet incomplete mathematical theory and a new derived unit of measurement, the "Clo" unit of thermal insulation. This monograph provides a practically painless introduction for the novice to the new science. The opening chapters are concerned with the purely physical and then physiological aspects of the problem; then follows a description and discussion of the various biological and artificial mechanisms developed by man to preserve constant the temperature of his "milieu intérieur". The final chapters are devoted to a consideration of the consequences resulting from failure to maintain this temperature. The subjects discussed range from the paradoxical disentropic behaviour of living cells to the cause and treatment of "Immersion Foot".

The authors' style is pleasant and lucid and the reviewer has found little to criticize on that score. As a clinician, however, he would have appreciated a further chapter dealing specifically with the reaction of the diseased subject to the temperature of his environment. Having experienced the immediate warming effect of the consumption of a block of chocolate in a sub-arctic environment the reviewer remains unconvinced that the specific dynamic action of food is of no importance in protection against cold.

There is in this monograph much of direct interest to the physiologist and the pathologist. The medical practitioner will find within it advice on the proper treatment of the casualty apparently frozen to death and it should be compulsory reading for those who practise that new, and as yet dangerous, therapeutic procedure, the induction of hypothermia.

A Manual of Anæsthetic Techniques. By William J. Pryor, M.B., Ch.B.N.Z., F.F.A. R.C.S. Eng., D.A.Eng., M.F.A., R.A.C.S. (Pp. x + 224; illustrated. 27s. 6d.) Bristol: John Wright & Sons Ltd. 1956.

Anæsthesia is predominantly a practical art, though, of course, a sound knowledge of pharmacology and the basic sciences is essential to its proper understanding and practice.

The author of this small book is concerned with this practical aspect, and his purpose is to provide, for junior trainees in the specialty, a vade-mecum where the answers may be found to the practical problems which arise in the day-to-day administration of anæsthetics.

The essentials of pre- and post-operative care are described together with detailed accounts of anæsthetic techniques suitable for most operations. Resuscitation is discussed, and the emergencies that may arise during the administration of an anæsthetic.

The risks of over-simplification have been largely avoided, in spite of the didactic style inevitable where much theoretical discussion has been deliberately omitted; and this work is not unsuccessful in fulfilling its author's intention. A minor fault is the haphazard use of pharmacological and proprietary names for drugs.

Biochemistry of the Eye. By Antoinette Pirie, M.A., Ph.D., and Ruth Van Heyningen, M.A., D.Phil. (Pp. viii + 323; illustrated. 35s.) Oxford: Blackwell Scientific Publications. 1956.

The object of this book is twofold; to interest biochemists in using the tissues of the eye for experimental purposes and to aid ophthalmologists in understanding the principles of ocular physiology and the biochemical aspects of pathological conditions. Certainly to the ophthalmologist this book fulfils its purpose admirably. The subject matter, ranging from the metabolism of ocular tissues to the ocular effects of nutritional diseases, includes chapters on the chemistry of vision, the vitreous body and, to a lesser extent, the aqueous humour. The first third of the book is concerned with the lens, and like the rest of the material is presented so clearly and interestingly that the rather formidable metabolic cycles are not too indigestible to an unchemically-minded reader. The chapter on experimental cataract is particularly interesting and serves to emphasize how much more work is required before the mechanism of senile cataract or its treatment by medical means is discovered. The metabolism of the cornea is well described and is of especial importance since corneal grafting has become a routine operative procedure. The response of the cornea to injury is also discussed.

The chapter on the chemical aspects of vision is concise and the subject is discussed with a healthy scepticism of the apparent simplicity of reactions *in vitro* of solutions obtained from retinal tissue by comparatively brutal methods of extraction.

Altogether the book provides a very interesting and readable account of the biochemistry of the eye. It is well printed and adequately illustrated.

Thiopentone and other Thiobarbiturates. By John W. Dundee, M.D., F.F.A. R.C.S., D.A. (Pp. viii + 312; illustrated. 22s. 6d.) Edinburgh and London: E. & S. Livingstone Ltd. 1956.

A recent advertisement by one of the manufacturers of thiopentone claims that this drug has been the subject of over 2,000 reports in the medical literature. Dr. Dundee gives the impression that he has read most of them; he certainly quotes several hundred references in this important and comprehensive monograph, wherein he correlates this previously scattered information for the first time.

There are excellent chapters on the distribution, effects and fate of the drug in the body, and those describing its clinical use contain much practical wisdom.

The history and technique of intravenous anæsthesia are discussed, and consideration is given to other recently introduced thiobarbiturates; appendices give valuable information on apparatus, the compatibility of thiobarbiturate solutions with other drugs, and methods of detecting and estimating thiopentone in body fluids.

This excellent book provides a balanced review of the present state of our knowledge of the pharmacology and clinical use of thiopentone, and authority is given to the opinions expressed by virtue of the author's own researches in this field.

The Practice of Medicine. Edited by John S. Richardson, M.V.O., M.A., M.D., F.R.C.P. (Pp. viii + 1076; illustrated. 40s. 0d.) London: J. & A. Churchill Ltd. 1956.

Many indeed are the standard textbooks of medicine for undergraduate students, and it might well be questioned whether there is, in fact, need for yet a further work. This new volume, emanating mainly from the staff of St. Thomas's Hospital, with an expert behind every chapter, presents an up-to-date series of contributions. It is particularly gratifying that this should cover not only the purely medical aspects, but also the social, economic and psychological factors.

Although there is no chapter on routine dermatology, one is at least happy to note that the dermatological aspects of systemic disease have not been excluded, since the skin as an index of systemic disease is an important factor in general medicine. The chapters on diseases of the heart and lungs are in the main excellent, and are illustrated throughout with negative X-ray prints, although it is a little difficult to understand why the publishers should, in some cases, have deemed a small, single print worth a whole page of art paper.

The contributions on neurology, psychiatry and endocrinology are to be commended, and in fact adequate space has been allocated to most subjects. As an exception, only 16 pages on the whole of the alimentary tract, compared with over 150 on the respiratory system, would seem quite out of proportion. The chapter on the important subject of the rheumatic diseases is somewhat scanty, in view of its great social and economic, as well as medical significance. It is a debatable point whether cervical spondylosis would not be better included in this chapter, rather than in the one on neurology. One would also question the accuracy of the statement that gold is of some value in 60% of cases of rheumatoid arthritis. The newer steroids might have been included in a 1956 textbook.

These considerations apart, the book is certainly to be recommended for those who seek a balanced, up-to-date review of the present situation in general medicine in its varied aspects.

A Textbook of Medicine. Edited by Russell L. Cecil, M.D., Sc.D., and Robert F. Loeb, M.D., Sc.D., D.Hon.Causa, LL.D. 9th edition. (Pp. xxxiv + 1786; illustrated. 105s.) Philadelphia and London: W. B. Saunders Company. 1955.

This well-known textbook, produced with the help of no fewer than 172 separate contributors, is a clear exposition of all the principal conditions met in the practice of clinical medicine. Each disease or syndrome starts with a simple definition, succeeded by a short historical note in smaller print. Ætiology, morbid anatomy, pathological physiology and chemistry, symptoms, diagnosis, prognosis, prophylaxis and treatment follow in logical order. At the end of each section there is usually a group of helpful references.

The subject matter is thus set out in a straightforward manner and along the lines to which we are accustomed. It is illustrated by just over 200 simple diagrams or X-ray reproductions, together with a small number of coloured plates. The description of the various diseases is straightforward, clear and concise and avoids controversial or abstruse problems. It is a book which can be strongly recommended to any senior undergraduate or recently qualified graduate who desires to keep his knowledge up to date and to read an American textbook which is on conventional lines and which is very easy to follow.

Section of Dermatology

President—LOUIS FORMAN, M.D., F.R.C.P.

[*May* 17, 1956]

Behcet's Syndrome and Thrombosis of Superior Vena Cava.—RONALD MAC KEITH, D.M., and LOUIS FORMAN, M.D., F.R.C.P.

This girl, aged 8, has a family history of tuberculosis. During a period of three years she has had ten attacks of what a number of physicians have called erythema nodosum. Today she has, as she has had before, little ulcers in the mouth; she also has a node on the shin. In the past she has had some pyrexia. An important point is that in some of the attacks of erythema nodosum there were tenderness and spasm of muscles, nearly always of the calf, once of the muscles of the left shoulder-joint. She had a positive 1/10,000 Mantoux test (but a later test with p.p.d. was negative). After she had been under our care some time she appeared to have enlarged paratracheal glands and because these in postprimary tubercle are by some considered to imply a bad prognosis, we gave her a course of streptomycin. A month after it was completed, she developed obstruction of the superior vena cava. A thoracotomy was made but no abnormality needing treatment was found.

When the case was described to the President he immediately recognized it as one of Behcet's Syndrome.

(*See* Harris, D., 1956, *Guy's Hosp. Rep.*, **105**, 213).

Dr. Louis Forman will publish a full account of the case.

Dr. P. J. Hare: I believe that in recent cases of this disease high blood fibrinogen levels have been observed, suggesting that thrombosis may play a part in the pathogenesis. On the other hand, cases have been treated in the past with anticoagulants but without benefit.

REFERENCE.—PALLIS, C. A., and FUDGE, B. J. (1956) *Arch. Neurol. Psychiat., Chicago*, **75**, 1.

Dr. J. G. Holmes: Dr. Duncan Evans of the Public Health Laboratory Service in Cardiff has isolated a virus from the retina of one case at post-mortem.

Discoid Lupus Erythematosus with Cryoglobulinæmia.—STEPHEN C. GOLD, M.A., M.D.

Mrs. M. D., aged 46, has attended St. John's Hospital for Diseases of the Skin under the care of Dr. Wigley since 1938 for chronic discoid lupus erythematosus affecting the hands and feet. Since then she has attended more or less regularly and has had courses of gold, bismuth, mepacrine and, recently, chloroquine. She suffers from general lassitude, vague aches in joints and muscles; she has always noticed that the cold weather brings out the skin eruption.

In 1953 she attended Moorfields Hospital for conjunctivitis; in 1954 she first developed purpura on her ankles; in the winter of 1955 a further episode of purpura followed the cold weather and, as a result, ulcers developed on the outer sides of both ankles. Throughout this period she was always found to have had a high sedimentation rate but L.E. cells have never been found.

She was admitted again in December 1955 with a recurrence of the rash on the hands and feet. There was a marked erythema associated with scaling and cracking. Purpura was evident around the feet and legs extending up to the thighs. There was a widespread, though mild, enlargement of lymphatic glands.

On examination.—She had an erythematous eruption of the face, in appearance and behaviour resembling rosacea. Fingers, hands, feet and toes showed chronic lupus erythematosus. On ankles and shins there was pigmentation remaining from previous purpura. Scars resulting from the ulcers were evident round the ankles. Lilac-coloured papules extended up the thighs.

Investigations.—E.S.R. 70 mm. in one hour (Wintrobe). Hb 62% (9·5 gram%). R.B.C. 3,100,000. W.B.C. 12,500. Normal differential, platelets 120,000. L.E. cells were not found on several examinations. Direct Coombs test negative. D.A.Test: Sensitized sheep cells positive in 1/2048. Urine contains albumin 1 gram in twenty-four hours. Serum proteins: Albumin 3·5, globulin 3·1 grams%, A/G ratio 1·2. Coagulation time 6½ minutes. Bleeding time 3½ minutes. Clot retraction good. Prothrombin time 12½ seconds. Cryoglobulins present. ECG: no abnormalities detected.

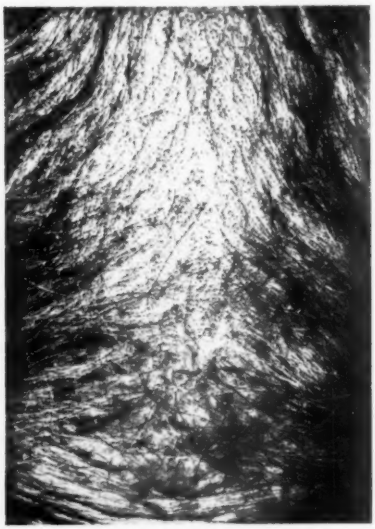
Course.—While in hospital she made no material improvement on simple bed rest, although ulcerated areas on feet and hands gradually healed. On February 29, 1956, a course of intravenous ACTH was started (15 units per day). This caused subjective improvement with no alteration of laboratory findings. On the fourteenth day she developed a fresh group of purpuric lesions, these coinciding with very cold weather.

POSTSCRIPT.—More recently there has been a fresh episode of purpura followed by skin ulceration for which she has been readmitted.

Bence-Jones protein was present in the urine for some ten days. There was no evidence of myelomatosis and presumably the Bence-Jones protein results from the breakdown of abnormal globulins.

Alopecia with Hyperkeratosis and Follicular Plugging of Scalp due to Hypothyroidism.—LOUIS FORMAN, M.D., F.R.C.P.

Mrs. E. P., aged 66.



Seven years' history of hair loss. The vertex of the scalp shows marked scaling with follicular hyperkeratosis (Fig. 1). The hair is thin, short and dry over the vertex and parietal areas. The skin over the arms and trunk is dry but no follicular plugging is to be demonstrated. Pulse 56 per minute. B.M.R. +27% (Normal +10½ to −10%).

ADDENDUM.—Thyroideum (B.P.) 2 grains daily for three weeks has led to a return of hair growth over the whole of the scalp, and disappearance of the follicular hyperkeratosis.

←FIG. 1.—Alopecia of vertex scalp with follicular hyperkeratosis.

Pulmonary and Cutaneous Sarcoidosis.—DENIS SHARVILL, M.R.C.P.

M. J. C., male, aged 26.

History of present illness.—In November 1954 he was treated in the Royal Victoria Hospital, Folkestone, and later in the Bow Arrow Hospital, Dartford, for a febrile illness with night sweats.

Clinical and radiological examination supported the diagnosis of pulmonary sarcoidosis. The spleen was palpable and superficial lymph nodes were enlarged; one of the latter from the neck showed on section a picture of typical caseating tuberculosis. Repeated attempts to find *M. tuberculosis* in sputa and gastric washings were unsuccessful. The Mantoux test was positive 1 : 100 and negative at 1 : 1,000.

From December 1954 to May 1955 he received antibiotics and chemotherapy, and from mid-May through August cortisone 100 mg. daily together with streptomycin and isoniazid. He felt much better and gained 2 st. in weight before starting the cortisone, which caused further subjective improvement and gave him a moon face, without any radiological change. He left hospital in December 1955 still taking isoniazid and P.A.S.

In April 1956 skin lesions were first noticed and chemotherapy was discontinued; he attended the skin clinic in May 1956.

Past history.—In 1947, at which time he was a radar operator, a routine mass miniature film showed suspicious loss of translucency in the second right interspace.

Family history.—An aunt had had pulmonary tuberculosis, but had never been in close contact with the patient.

On examination.—Very numerous nodules were present in the skin especially on the proximal limbs, but no part was spared. They varied in size from 0·5 to 2 cm. and were

strikingly hard on palpation. There was no change in the overlying epidermis and their colour was a dusky purple; on diascopy a brownish-yellow tinge was seen. Small nodules were present in the lower palpebral conjunctivæ. Superficial lymph nodes were still enlarged and the spleen palpable.

There was no radiological evidence of bone involvement. Serum proteins were normal. Biopsy of a skin nodule showed a histological picture typical of sarcoid.

POSTSCRIPT (September 1956).—Patch tests with beryllium chloride were negative at forty-eight hours and three weeks (Sneddon, 1955).

In September 1956 it was thought that there was some regression of the skin lesions, but this was not striking. The fibrosis of the lungs was unchanged.

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SNEDDON, I. B. (1955) *Brit. med. J.*, i, 1448.

[*June* 21, 1956]

Lipid Electrophoresis Patterns in Xanthomatosis

By W. G. DANGERFIELD, Ph.D., L.R.C.P., M.R.C.S.

North Middlesex Hospital, London.

THE lipid substances present in blood plasma are not dispersed as individual molecules, but are built up into complex lipid particles having a hydrophilic or "water-soluble" outer layer. The nature, composition and variation in these lipid complexes are now being widely investigated by various means—by chemical separation, ultracentrifugation and by electrophoresis both in the Tiselius apparatus and on paper.

The technique of paper electrophoresis is simple and the apparatus required inexpensive. However, considerably more skill and practice is required for making good lipid patterns than is needed for making good protein patterns. After electrophoresis the strip is cut lengthwise into two unequal portions, the narrower strip is stained for protein and the wider one for lipid. The author uses Light Green SF for staining protein and Sudan Black in 55% alcohol for lipid (Dangerfield and Smith, 1955).

Normal serum gives a pattern (Fig. 1) showing three main components namely:

α–lipoprotein—a rather diffuse band level with α_1–globulin.

β–*lipoprotein*—a sharp dense band level with β–globulin

and a "*fatty trail*" extending from the line of application (origin O) up to, and sometimes

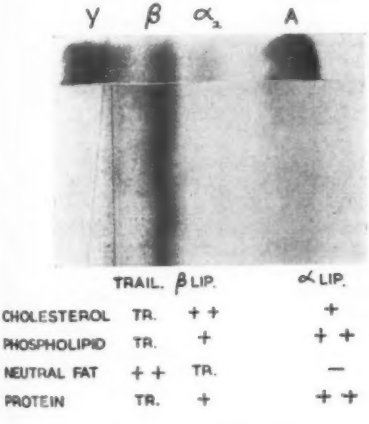


FIG.1.—Normal serum.

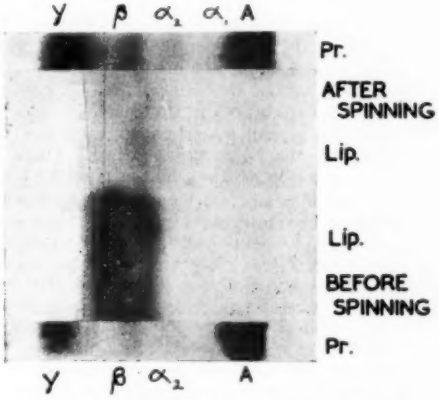


FIG. 2.—Hyperlipæmic serum before and after centrifuging.

in front of, the β-lipoprotein. There is no accepted name for this trail, which is variously ascribed to chylomicrons or to tailing of the β-lipoprotein; it is almost certainly in large part due to particles, microscopic and submicroscopic, rich in neutral fat.

In addition to these three bands there is sometimes staining elsewhere, e.g. level with the albumin (*lipalbumin*) which may be due to free fatty acid adsorbed on albumin, and in a few cases a narrow zone of staining is seen ahead of the β-lipoprotein. This zone of

pre-β-lipid is markedly increased in density in nephrotic sera and moderately increased in many case of coronary infarction.

The composition of the lipid complexes giving rise to the main bands is crudely indicated in Fig. 1 and more precisely in Table I. It is difficult to give any accurate analysis of these

TABLE I.—LIPID COMPLEXES IN SERUM

	Cholesterol		Phospholipid		Neutral fat	Protein or peptide	Density	S_f No.
	Total	F/T	Total	C/P				
	%		%		%	%		
α–Lipoprotein ..	20	0·2	25	0·5	tr.	50	1·07–1·12	—
β–Lipoprotein ..	50	0·25	25	1·3	tr.	20	1·03–1·04	4–8
Chylomicrons ..	c. 7	—	c. 7	—	85	tr.	c. 0·95	up to 40,000
Intermediate lipids (S_f 10–100) ..	Intermediate between chylomicrons and β–LP.						0·95–1·02	10–100
Lipids of biliary cirrhosis ..	20	0·95	50	0·45	5–20	tr.	1·04	5–30

The column headed F/T gives the ratio free cholesterol/total cholesterol.
The column headed C/P gives the ratio cholesterol/phospholipid by weight.
The apparent discrepancy between the C/P ratio given in the fourth column and that calculated from the figures in the first and third columns arises mainly because the weight of the fatty acid combined with the cholesterol is included in the first column, but not in the C/P column.

complexes (which may not be of absolutely fixed composition) because the figures given by different authors vary considerably—*see* Oncley *et al.* (1950), Oncley and Gurd (1953), Barr *et al.* (1953) and Bragdon *et al.* (1956). The approximate figures given here will serve as a basis for considering the lipid disturbances found in xanthomatosis.

A lipæmic serum gives a pattern with a trail of increased density. In ordinary transient alimentary lipæmia the β-lipoprotein band can still be discerned, being considerably more densely stained than the trail, but in gross lipæmia, as in essential hyperlipæmia, the β-lipoprotein band is obliterated. If a lipæmic serum is centrifuged at high speed (say at 10,000 r.p.m. in a small centrifuge for one hour) the fat particles rise to form a cream leaving a clear or almost clear serum below. Fig. 2 shows the patterns obtained from a lipæmic serum, before and after centrifuging. In this case very little α and β-lipoprotein is seen even in the centrifuged specimen—this may be because they were originally present in the serum in diminished quantity or because they were adsorbed on to the fat particles, and so removed.

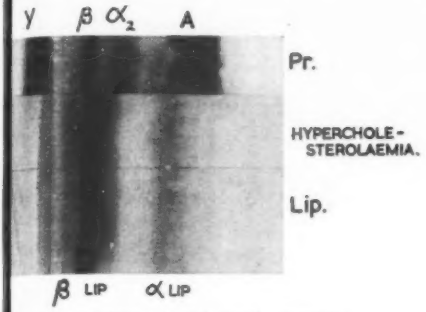
On examining the pattern prepared from the sera of patients with xanthomatosis it is found that the great majority fall into the three classes as follows:

(*a*) The typical hypercholesterolæmic pattern (Fig. 3A) is characterized by a very dense β-lipoprotein band, not much wider than usual. There were 4 patients in this class; their sera were almost always clear and they all gave a family history of xanthomatosis or early coronary thrombosis or both.

(*b*) The typical hyperlipæmic pattern (Fig. 3B) has a very dense and wide trail which obliterates the β-lipoprotein band. There were 3 patients in this group; their sera were always extremely turbid, and in one case the serum sometimes formed a cream on standing.

(*c*) An intermediate type of pattern occurs in which both β-lipoprotein and the trail are of increased density. There were 5 patients who produced this type of pattern, 2 had clear sera, 1 slightly turbid, and 2 moderately turbid sera. There was also one patient whose serum was clear and produced a typical hypercholesterolæmic pattern at the first two examinations about three years ago, but it gradually became moderately lipæmic and now produces an intermediate type of pattern.

In addition to these there was one patient whose serum produced a unique pattern. This patient is a boy aged 20 months who is slightly jaundiced and appears to have biliary cirrhosis due to reticulo-endotheliosis of the Letterer-Siwe type, He has recently developed cutaneous xanthomas presumably as a consequence of high plasma lipid levels. The serum was jaundiced and clear when fresh, but after freezing it was grossly turbid. The patterns given before and after freezing are strikingly different (Fig. 4A and B). The fresh serum shows a wide band of γ_1-lipoprotein (or possibly β_2-lipoprotein). Note that there is no appreciable staining at the site of application (O) and there is no α-lipoprotein band visible. After freezing and thawing the lipid has been rendered insoluble and it simply deposits at the site of application (O). There is only a weak band of β-lipoprotein showing. Provisional analysis of this child's serum showed 5,500 mg.% total lipid, 1,400 mg.% cholesterol and 3,000 mg.% phospholipid. A short clinical account of this case with a more complete analysis will be published elsewhere, but it is likely that the



A.—Hypercholesterolæmic xanthomatosis.

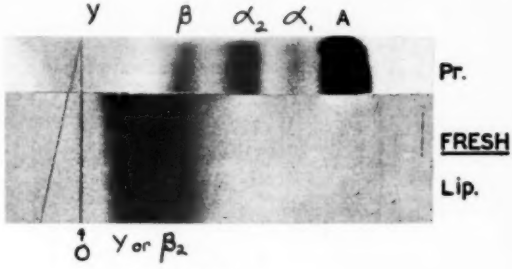


FIG. 4A.

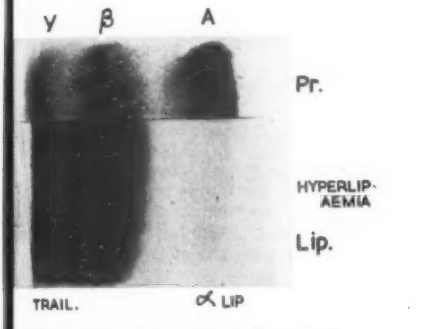


FIG. 3B.—Hyperlipæmic xanthomatosis.

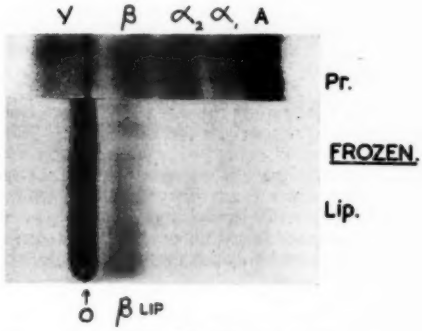


FIG. 4B.

FIG. 4 (A and B).—Biliary cirrhosis with latent lipæmia.

lipid complex present in this case is the same or related to the lipid complexes found in the other cases of biliary cirrhosis that have been studied by Ahrens and Kunkel (1949), by Russ *et al.* (1956), by Lever and Hurley (1953), and by McGinley *et al.* (1952). These authors find that the phospholipid in these cases is remarkably high, and that the cholesterol is largely free. Thannhauser (1950) also describes such cases and gives similar analyses. All authors agree that the sera in these cases are usually clear though they do not state specifically whether freezing alters them; they differ in their opinion of the amount of neutral fat present. The present author has previously found another jaundiced serum that was clear when fresh but went grossly turbid after freezing. This serum was from an old man who had had a carcinoma of the colon removed two years previously and had developed a secondary growth in the clavicle and jaundice; the serum cholesterol was 550 mg.%. The cause of the jaundice was not established, but he was still jaundiced and had a large liver when he died at home three months later. Many other jaundiced sera have been frozen, but none became grossly turbid.

A few experiments were carried out to investigate the action of intravenous heparin on the lipids of 2 of these patients, one a hypercholesterolæmic case, the other a lipæmic case. The changes produced in the lipid patterns were similar to those that occur in the majority of normal persons.

The foregoing observations pose the following questions:

(1) Is there really an intermediate or mixed type of xanthomatosis?

(2) Can hypercholesterolæmia gradually give rise to a secondary lipæmia?

(3) Is the low α-lipoprotein frequently seen in hyperlipæmia, and sometimes in hypercholesterolæmia real, and is it connected directly or indirectly with the increase in the main lipid?

(4) More fundamentally—what are the underlying biochemical lesions in each type of xanthomatosis?

When pondering these questions it is well to remember that biochemists have recently shown that living cells can convert active acetic acid (i.e. acetyl-coenzyme A) into fatty acid, or into cholesterol, or oxidize it to CO_2 and H_2O via the citric acid cycle. These reactions seem to occur with great ease in the living cell.

In conclusion it would seem desirable to separate the lipid complexes by some physical method (e.g. precipitation, high speed centrifugation, ultracentrifugation or electrophoresis) prior to determination of the individual constituents such as cholesterol and phospholipid. This is the trend of present research work on serum lipids.

I wish to thank Dr. E. B. Smith for her assistance in this work.

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Essential Hyperlipæmia and Primary Hypercholesterolæmia

By P. A. J. SMITH, M.B., M.R.C.P.
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MY remarks are confined to xanthomatosis associated with a raised blood cholesterol level and I am not concerned with the so-called disseminate xanthomas of the Hand-Schüller-Christian and related syndromes. I use the term hyperlipæmia to signify an increased amount of neutral fat, and neutral fat only, in the blood; and this can be detected by naked-eye inspection of the plasma which appears opalescent or frankly milky.

CLINICAL ASPECTS

The following superficial lesions are associated with hypercholesterolæmia: Xanthelasma palpebrarum, tuberous xanthoma, eruptive or papular xanthoma, plane xanthoma, and tendon xanthoma.

With one possible exception these lesions signify a present or past elevation of blood cholesterol. The exception, xanthelasma palpebrarum, is often reported in the absence of hypercholesterolæmia—at least on one examination. But before regarding it as a purely local condition it is necessary to have repeated blood examinations, and to examine members of the family for manifestations of hypercholesterolæmia.

Hypercholesterolæmia may be a primary condition which is often familial, and it may be secondary to biliary cirrhosis. It may be associated with hyperlipæmia, which in turn can be idiopathic or secondary to diabetes, subacute nephritis and possibly recurrent pancreatitis. I want to consider only the two relatively common primary types of xanthomatosis—familial hypercholesterolæmia and essential hyperlipæmia (Table I).

TABLE I.—HYPERCHOLESTEROLÆMIC XANTHOMATOSES

	Cholesterol	Phospholipids	Neutral fats
Primary familial	+	+	N
Biliary cirrhosis	+	++	N
Hyperlipæmia:			
Idiopathic	+	+	+
Diabetes	+	+	+
Nephrosis	+	+	+
? Chronic pancreatitis	+	+	+

Although essential hyperlipæmia has been recognized by foreign physicians for over twenty years, it has not yet found a place in English textbooks of medicine. Dermatologists have not distinguished its cutaneous manifestations from those of the commoner primary familial hypercholesterolæmia; they have lumped both groups together, called them xanthoma tuberosum, and left it at that. 95 cases have been reported, and they include 14 families. The commonest presenting symptoms are recurrent attacks of upper abdominal pain, and xanthomas. Many are free from symptoms and have been detected on examination of the blood for some other investigation since opalescence of the fasting serum is the hall-mark of the disease. Enlargement of the liver and/or spleen occurs in about 25% of cases. Coronary occlusion was thought not to occur in this condition until Dr. Lever and I (Lever *et al.*, 1954) reported it in 4 of our 7 cases. Since then 22 more instances

have been reported (Malmros *et al.*, 1954; Adlersberg, 1955; Martt and Connor, 1956) including one death from cardiac infarction in a man of 32 years (Table II).

TABLE II.—ESSENTIAL HYPERLIPÆMIA
95 CASES

Families	14	Coronary disease	26
Milky serum	95	Hepatomegaly	26
Xanthomas	44	Splenomegaly	24
Abdominal pain	32	Glycosuria	13

TABLE III.—LESIONS IN XANTHOMATOSIS

	Hypercholesterolæmia 15 cases	Hyperlipæmia 9 cases
Xanthelasma palpebrarum	13	1
Tuberous xanthomas	3	6
Eruptive xanthomas	0	6
Plane xanthomas of palms	1	4
Tendon xanthomas	9	4
Coronary disease	5	3

As far as cutaneous lesions are concerned Thannhauser (1950) maintained that it is possible to distinguish hyperlipæmia from primary hypercholesterolæmia. In the first condition there are on the buttocks and extensor aspects of the limbs small papular or eruptive xanthomas often looking like pustules with an erythematous halo, in contrast to the larger nodules of xanthoma tuberosum found on the elbows and knees in primary hypercholesterolæmia. I have not found this distinction altogether valid, and in the 24 cases of xanthomatosis I have watched in Boston and Whitechapel the lesions were as shown in Table III.

Thus while eruptive xanthomas occur only in hyperlipæmia, they are not found in every case. Eyelid lesions were seen in most cases of hypercholesterolæmia but also in one case of hyperlipæmia. Xanthomas of tendon sheaths appeared in both groups most commonly as a diffuse thickening of the Achilles tendons and as localized nodules on the extensor tendons of the hands. Less often the patellar tendon was thickened at its tibial attachment, the triceps at its insertion into the olecranon and the peroneal tendons lateral to the ankle. In the cases of hypercholesterolæmia referred to us from the cardiac department the superficial lesions were invariably of the eyelids and tendons, while tuberous xanthomas were absent.

ANALYSIS OF BLOOD LIPIDS

Cholesterol, phospholipids and fatty acids were measured in 5 normals, 5 cases of essential hyperlipæmia and 5 cases of hypercholesterolæmia, and from these figures we calculated the neutral fat content. The results are shown in Table IV.

TABLE IV

Cholesterol mg.%			Phospholipid mg.%			Neutral fat mg.%		
Normal	Hypercholesterolæmia	Hyperlipæmia	Normal	Hypercholesterolæmia	Hyperlipæmia	Normal	Hypercholesterolæmia	Hyperlipæmia
170	528	1,000	175	360	1,110	31	133	3,005
270	403	730	275	399	563	72	252	2,270
210	427	667	260	331	607	0	144	940
315	489	575	312	397	532	82	136	994
280	400	622	290	358	523	57	139	1,000
Average values			Average values			Average values		
249	449	719	262	369	667	48	161	1,642

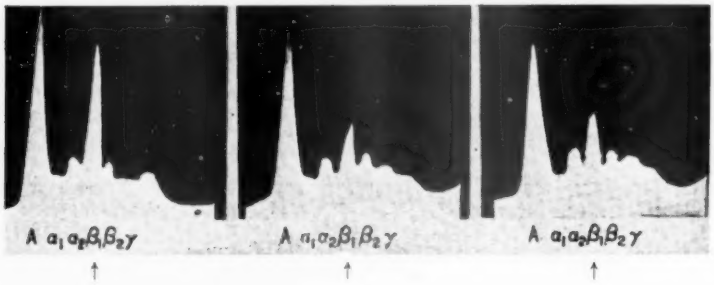
We also measured the turbidity of each plasma in a Klett colorimeter and found it was roughly proportional to the amount of neutral fat present; though perhaps a more constant relationship existed between turbidity and the neutral fat/phospholipid ratio. This would support the often quoted view that the opalescence of the serum in the xanthomatoses depends on the relative amount of phospholipid present and explains why the serum is clear, though jaundiced, in the xanthomatosis of biliary cirrhosis.

ELECTROPHORESIS

Using a Tiselius apparatus we found a high β_1 peak in hypercholesterolæmia, while in hyperlipæmia there was an increase in α_2 and sometimes β_1 as well. High-speed centrifugation, (18,000 r.p.m. for one hour) had no effect on the pattern in hypercholesterolæmia but in hyperlipæmia it caused considerable reduction in the α_2 (and β_1) peaks as well as reducing the turbidity. Rotation of the plasma with ether at 5° C. for thirty minutes (and subsequent slow centrifugation to remove the ether layer) reduced the α and β peaks to normal and made the serum perfectly translucent. These observations suggested that the high α_2 and β_1 peaks were caused by lipid and we confirmed this by fractionating each plasma according to the method of Cohn in a cold ethanol bath at −5° C. The cholesterol and phospho-

lipids were then estimated in each fraction and were found to be concentrated in those fractions which contain the α_2 and β_1 lipoproteins (Figs. 1 and 2).

PRIMARY HYPERCHOLESTEROLÆMIA



ESSENTIAL HYPERLIPÆMIA

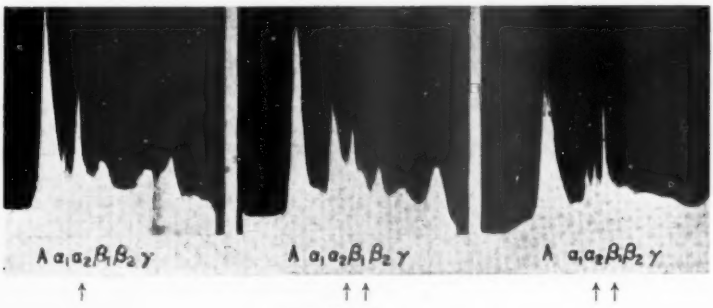


FIG. 1.

FAT TOLERANCE CURVES

Another distinction between the two types of xanthomatosis was reported by Lever and Waddell (1955). They gave an intravenous infusion of 500 c.c. of a 10% cotton-seed oil emulsion and estimated the blood lipids at regular intervals for twenty hours. In each of 4 cases of hypercholesterolæmia and in 10 of 14 normal controls the neutral fat had returned to its fasting level by the end of six hours; while in 8 out of 9 cases of hyperlipæmia the level was still raised at that time, indicating a delay in removal of fat from the blood stream in these cases. He also reported the effect of these single infusions on the blood cholesterol. In all subjects where the initial level was over 300 mg. % (normals, hyperlipæmia and hypercholesterolæmia) there was an average decrease of about 100 mg. % by the end of twenty hours. Even in normals with an initial cholesterol of less than 300 mg. % it was still reduced, but to a lesser degree.

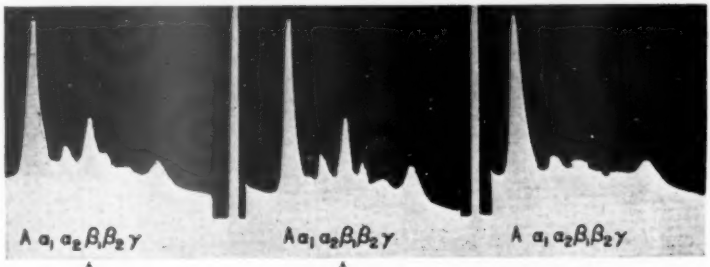
EFFECT OF PROLONGED ADMINISTRATION OF UNSATURATED FATTY ACIDS

Daily infusions of the cotton-seed oil emulsion were given for a week and this caused a lowering of the blood cholesterol in both types of xanthomatosis as well as the neutral fat in hyperlipæmia. The reduction was short-lived and the levels began to rise again a week after the last infusion. This response is particularly interesting in the light of the recent paper by Brontë-Stewart *et al.* (1956) on the effect of unsaturated vegetable and marine oils on blood cholesterol.

THE EFFECT OF HEPARIN

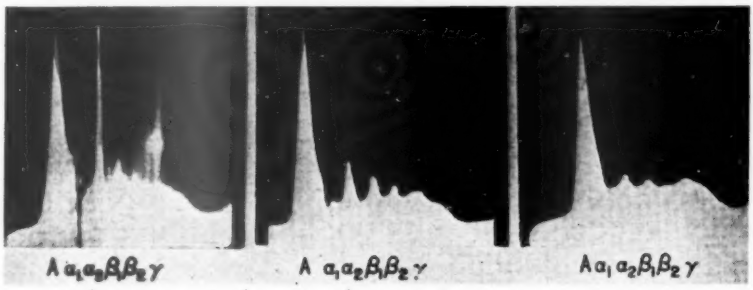
It has been known for years that heparin, given intravenously, reduces the physiological hyperlipæmia which occurs two to three hours after a fatty meal, and we wanted to know what its effect would be on the turbidity and electrophoretic pattern in cases of essential hyperlipæmia. We therefore gave 50–100 mg. of heparin intravenously and took blood

PRIMARY HYPERCHOLESTEROLÆMIA



native plasma 18,000 r.p.m. ether extraction

IDIOPATHIC HYPERLIPÆMIA



native plasma 18,000 r.p.m. ether extraction

FIG. 2.

TABLE V.—EFFECT OF INTRAVENOUS HEPARIN

	Turbidity	Electrophoretic pattern
7 Normal subjects ..	i.s.q.	5 i.s.q. 1 β_1 smaller, A and α_1 increased 1 β_1 smaller, α_2 increased
8 Hypercholesterolæmia	i.s.q.	2 i.s.q. 6 β_1 smaller, A and α_1 or α_2 increase
6 Hyperlipæmia ..	slight decrease	6 α_2 or α_2 and β_1 became normal, pre-albumin peak appeared

samples fifteen minutes later. The results are as shown in Table V and electrophoretic patterns (Fig. 3).

High-speed centrifugation reduced the size of the pre-albumin peak and ether extraction removed it completely—in fact it behaved just as did the raised α_2 and β_1 peaks of non-heparinized hyperlipæmic plasma. It thus looks as though heparin combines with lipid, and by breaking up the α_2 and β_1 lipoproteins restores the protein components of these peaks to their normal level. Because of the high negative charge of heparin the newly formed heparin-lipid complex has a higher speed of migration in the electrophoretic field and therefore appears in front of the albumin peak.

SUMMARY

When xanthomatosis with a raised blood cholesterol is not secondary to diabetes, liver disease, kidney disease, hypothyroidism or pancreatitis it is found in two distinct conditions—primary familial hypercholesterolæmia (which is generally recognized) and essential hyperlipæmia (which is not). In the absence of eruptive xanthomas there is nothing to distinguish hyperlipæmia by looking at the skin, though inspection of the fasting plasma will reveal its opalescence. The two diseases differ in their ranges of blood lipid levels, electrophoretic patterns, fat tolerance and response to heparin.

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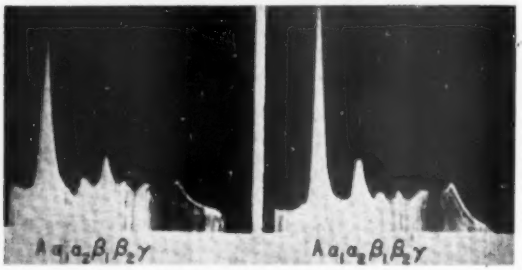

ESSENTIAL HYPERLIPÆMIA

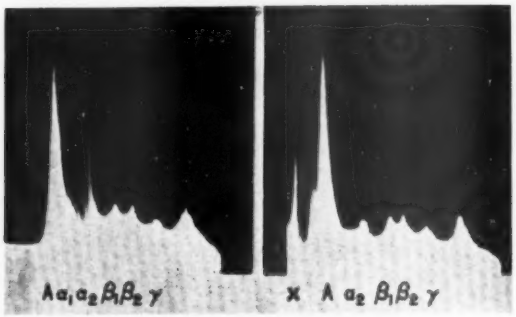

FIG. 3.

Figs. 1, 2 and 3 are taken from (1954) *Journal of Investigative Dermatology*, **22**, pp. 57 *et seq.*, by kind permission.]

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Familial Xanthomatosis

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E. GRAHAME JONES, M.B., M.R.C.P., *Royal Gwent Hospital, Newport*
and P. G. WELLS, M.B., Ch.B., D.C.H., D.R.C.O.G., *Hammersmith Hospital, London*

IT is the purpose of this paper to illustrate, very briefly, some of the clinical, biochemical, and, in particular, the genetic aspects of familial xanthomatosis.

The clinical features of xanthomatosis are well known but I would like to make brief reference to the corneal or lipoid arcus (Fig. 1). This is not only a common feature of the syndrome, but it is also one of two lesions which may be reproduced in the cholesterol-fed animal. When found in young victims of coronary disease it should suggest a background of essential hypercholesterolæmia.

Opinions of the genetic formula of this disease are not unanimous; the current view, held by Wilkinson and others (1948), and Adlersberg and his associates (1949), is that hypercholesterolæmia is transmitted as an incomplete dominant, without sex linkage. It will be appreciated, however, that in formulating such a transmission, investigators have used various methods for cholesterol estimation, and accepted different critical levels for assessing hypercholesterolæmia. None apparently has appreciated the fact that the blood cholesterol varies with age. It is because of this that the range for normal cholesterol used in this investigation is that published by Keys and others (1950), who conducted an extensive

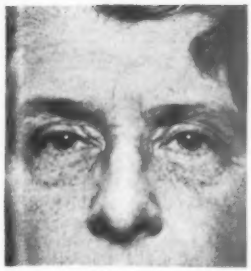
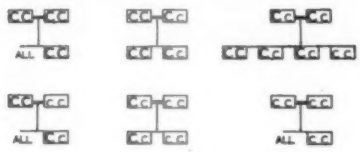


FIG. 1.—Patient showing both corneal arcus and xanthelasma.

investigation on blood cholesterols in normals in age groups ranging from 17 years to 70 years (Fig. 9).

Fig. 2 summarizes the possible matings and predicted offspring in familial xanthomatosis; the diagram is modified from Wilkinson and others (1948) who suggested that primary xanthomatosis was the homozygous abnormal state for cholesterol and not merely a chance occurrence within a family with essential hypercholesterolæmia. It will be seen that there are two possible abnormal states for cholesterol, the heterozygous abnormal, expressed clinically as essential hypercholesterolæmia alone, and the homozygous abnormal, recognized clinically as the full syndrome of hypercholesterolæmia, xanthomatosis, and, almost invariably, myocardial ischæmia. The familiar formula then follows, and, as illustrated, patients with xanthomatosis should have resulted from the mating of parents both of whom carry an abnormal gene for cholesterol.



c Normal blood cholesterol.
C Hypercholesterolæmia.
cc Homozygous normal.
Cc Heterozygous abnormal (essential hypercholesterolæmia).
CC Homozygous abnormal (xanthomatosis)

FIG. 2.—The possible matings and their offspring in essential hypercholesterolæmia modified from Wilkinson and others (1948).

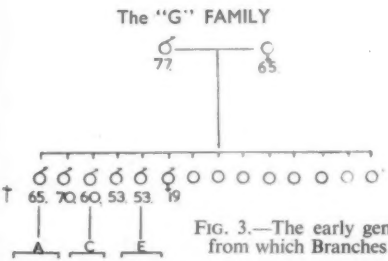


FIG. 3.—The early generation of the "G" family from which Branches E, A, and C are derived.

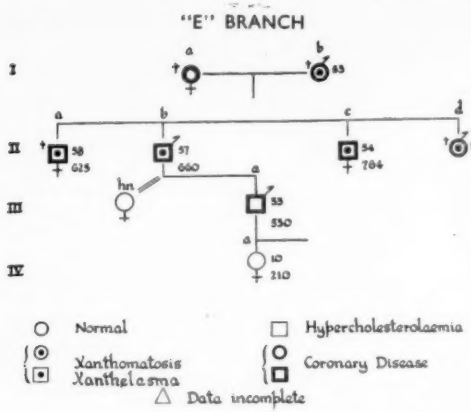
The first pedigree investigated (Fig. 3) was a large one, and we know little about this early generation. It was possible, however, to trace from it three branches; unfortunately the tree so produced is too large to illustrate on one diagram, so that they will appear as branches E, A and C (Figs. 4–6).

Within these three branches we know something of 110 members of whom 83 are said to be living, but are scattered widely over Great Britain and the Commonwealth. We have been able to obtain blood samples from 56 of the 60 members who have been traced.

The original patient (IIa) was 1 of 4 siblings (Fig. 4) all of whom have, or had, gross xanthomatosis; all 4 suffered for years with ischæmic heart disease, with episodes of myocardial infarction which proved fatal in two (IIa and IId). Three siblings are known to have had hypercholesterolæmia, and it seems very probable that the fourth would have shown this abnormality. In the first generation, the father (Ib) was known to have had xanthomatosis, and to have died, at the age of 53, of a coronary occlusion. There is much less information about the mother (Ia), except that she is said to have died of heart disease. In the third generation, the son (IIIa) at 33 years of age, already receives treatment for angina, and has hypercholesterolæmia. His daughter (IVa), representing the fourth generation at 10 years of age is symptomless and has a normal cholesterol.

The genetic interpretation of this branch is that the father (Ib) was a homozygous abnormal, from a family with essential hypercholesterolæmia and appears to have mated with at least a heterozygous abnormal (Ia) to produce a sibship of 4 apparently homozygous abnormal siblings. The only productive mating in the second generation, between a homozygous abnormal (IIb) and a homozygous normal (hn) resulted in a heterozygous abnormal sibling (IIIa) with hypercholesterolæmia. This branch stimulated our interest in the other much larger sections of the family.

Although we have failed to find any further examples of xanthomatosis, the homozygous abnormal state, in "A" branch (Fig. 5) it will be seen that there is evidence of xanthelasma in the second and third generations. Hypercholesterolæmia appears in the second, third and, we think, in the fourth generation, and has followed a predictable transmission. With the exception of the kindred (IIi, IIIk and IVr), this branch is genetically compatible with a dominant penetrance. Coronary disease is depicted where the history is strongly suggestive, but the diagnosis often lacks objective proof.



←FIG. 4.—"E" Branch of the first, or "G" family. The symbols used throughout these pedigrees, although not conventional, are retained for clarity, and for comparison with the large families published by Adlersberg and others (1949) and Adlersberg (1951). Generations are signified by Roman numbers, and individual members alphabetically, throughout each generation. The symbol + means that the member is deceased. Plasma cholesterols are recorded.

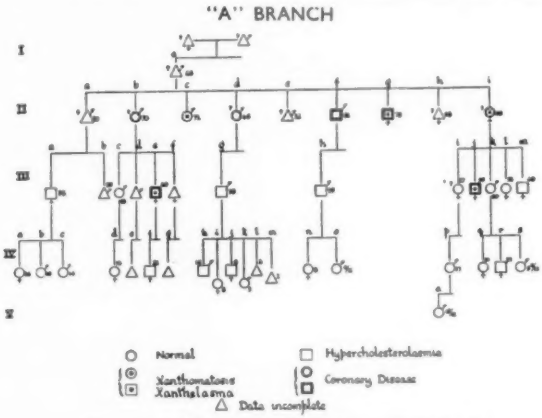


FIG. 5.—"A" Branch of the first or "G" family.

In "C" branch (Fig. 6) evidence of the syndrome is slight. We have recorded hypercholesterolæmia in only 3 instances, but it is notable that xanthelasma has appeared in the second and third generations and death from coronary disease at an early age in both second and third generations. In this respect the sibship (IIIj, k, l, m) is of interest because the mother (IIe) died at 34 years of age and her daughter (IIIk), who died at 27 years of age, was found at autopsy to have gross coronary disease.

The examination of the second family is not yet complete, but sufficient evidence is available to shed further light on the transmission of the disease (Fig. 7).

The first member of this family encountered was a girl (IIIb), known to have had angina since the age of 16 years, and now showing electrocardiographic evidence of coronary occlusion. She has gross xanthomatosis and hypercholesterolæmia, in fact a homozygous abnormal. Her sister (IIId) had presented an identical picture, with florid xanthomatosis, and died at the age of 21 years of a coronary thrombosis after many years of intractable angina. It is of interest to note here that she also had aortic incompetence, and her sister (IIIb) now has a rough systolic murmur compatible with a diagnosis of aortic stenosis suggesting the presence in both of xanthomatous valvular disease. A sister (IIIe) though symptomless has hypercholesterolæmia, but the brother (IIIc) on present evidence is normal.

Further investigation of this family appeared promising, because the occurrence of 2 members with xanthomatosis in the sibship implied that both parents would have hypercholesterolæmia. It was, therefore, not surprising to find that this sibship sprang from a consanguineous marriage within a family with essential hypercholesterolæmia. Little is known about the first generation at the moment, but information concerning the second generation is more complete, and as will be seen there is good evidence of xanthelasma, hypercholesterolæmia, and coronary disease.

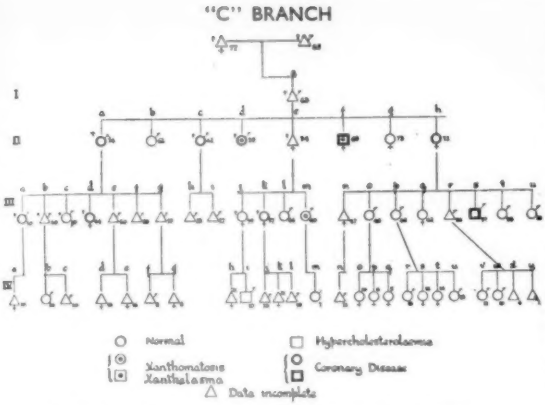


FIG. 6.—"C" Branch of the first or "G" family.

Both parents of the sibship (IIIb, c, d, e) as predicted, have hypercholesterolæmia; the father (IId) has gross xanthelasma and has had a myocardial infarction, the mother (IIe) is otherwise healthy.

A genetic interpretation of this pedigree, like the first, would be in keeping with the formula already expressed.

The third family is much smaller (Fig. 8), and the first member encountered was the patient (IIb), admitted following a coronary thrombosis. She had xanthomatosis, xanthelasma, and marked hypercholesterolæmia. A brother (IIa) died of heart disease, and the remaining siblings (IIc and IId), although symptomless, have hypercholesterolæmia. In the first generation there is evidence of xanthelasma and coronary disease. Therefore, although it may be concluded that this patient comes of a family with essential hypercholesterolæmia, this pedigree is too small to establish a genetic pattern.

BIOCHEMISTRY

The results of the total plasma cholesterol estimations in these families are recorded (Fig. 9) to illustrate the frequency of xanthomatosis, xanthelasma, and coronary disease in those members with a raised plasma cholesterol. The interrupted line "b_1 . . . . . 98%", represents the maximum plasma cholesterol level, in each age group from 17 years to 75 years, for 98% of a normal population studied by Keys and others (1950).

The occasional association of hyperuricæmia and xanthomatosis (Fig. 10), has been recorded once before (Adlersberg, 1949). It will be seen that all those with a raised uric acid level also have hypercholesterolæmia. There appears to be no clear explanation for the association of these two metabolic disturbances, but we intend to investigate this point in greater detail.

Paper electrophoresis for plasma proteins and lipoproteins has been performed on

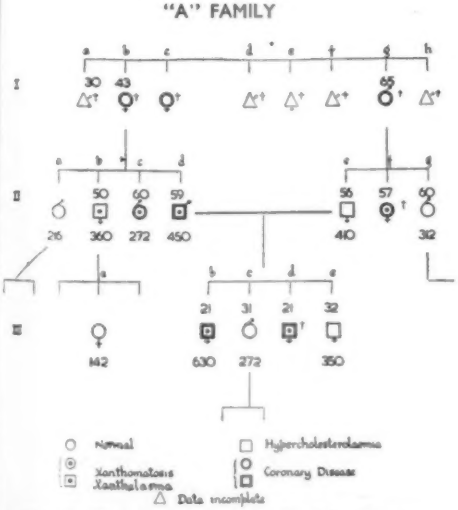


FIG. 7.—The second or "A" family. Plasma cholesterols are recorded.

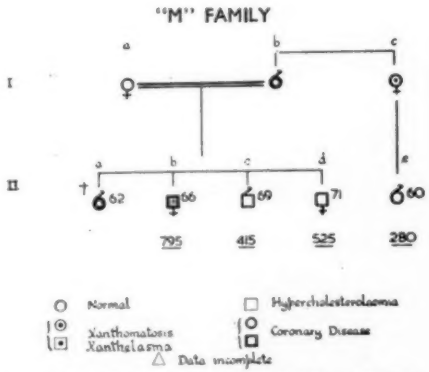


FIG. 8.—The third or "M" family. Plasma cholesterols are recorded.

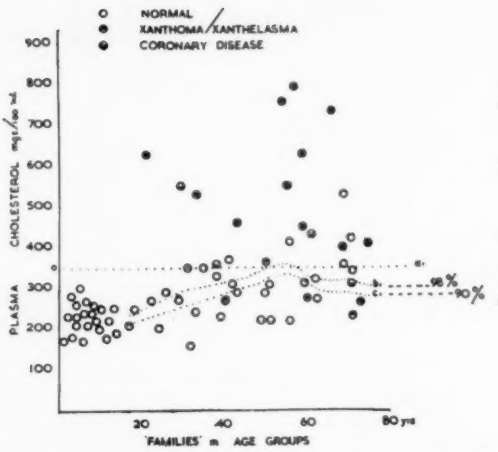


FIG. 9.—Plasma cholesterol estimations in members of all three families; it will be seen that in most cases with hypercholesterolæmia there is evidence of xanthomatosis or xanthelasma, and of coronary disease, and very frequently a combination of both. Plasma cholesterol was estimated by the methods of Clarke and Marney (1945) and Bloor (1916).

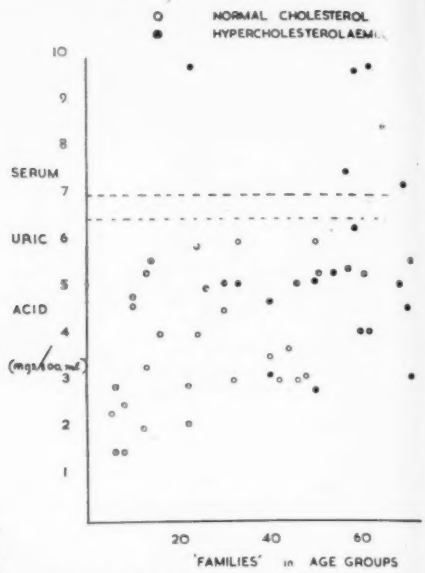


FIG. 10.—The occasional association of hyperuricæmia with hypercholesterolæmia is shown. Hyperlipæmia may depress uric acid excretion (Adlersberg, 1949).

almost all members of these families, and has frequently revealed the intense β-lipoprotein band characteristic of this syndrome.

TREATMENT

A brief reference to treatment is included merely to record our experience with the compounds triiodothyroacetic acid (triac) and tetraiodothyroacetic acid (tetrac), which have been shown to lower the blood cholesterol before materially affecting the basal metabolic rate (Trotter, 1956; Goolden, 1956). Neither compound appears to maintain a significant reduction of the blood cholesterol in patients with xanthomatosis.

CONCLUSIONS

The principal objective of this investigation was to outline the genetic pattern of essential hypercholesterolæmia, a subject which has received extremely scant attention in this country.

Our results confirm that essential hypercholesterolæmia is transmitted as a dominant, and appear to support the view expressed by Wilkinson and others (1948) that primary hypercholesterolæmic xanthomatosis represents the homozygous abnormal state.

The investigation has revealed again the high incidence of coronary disease found in families with essential hypercholesterolæmia, and has shown it to be an almost invariable feature of hypercholesterolæmic xanthomatosis.

ACKNOWLEDGMENTS

We are indebted to Dr. C. E. Davies and Dr. James Brown for permission to publish cases under their care. For their invaluable help we would also like to express our gratitude to Drs. A. Jordon, T. L. Morris and F. Young, and to Mr. G. A. Cheyne. For the illustrations we thank Mr. Foster, medical artist, and the Photographic Department of the United Sheffield Hospitals. We are grateful to Mrs. Rosalind Pitt-Rivers for supplies of tetrac, and Glaxo Laboratories for supplies of triac.

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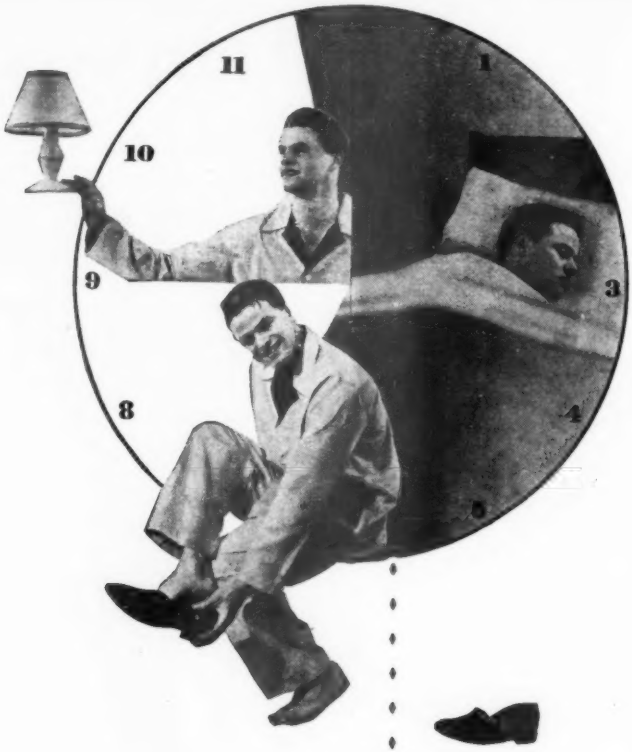

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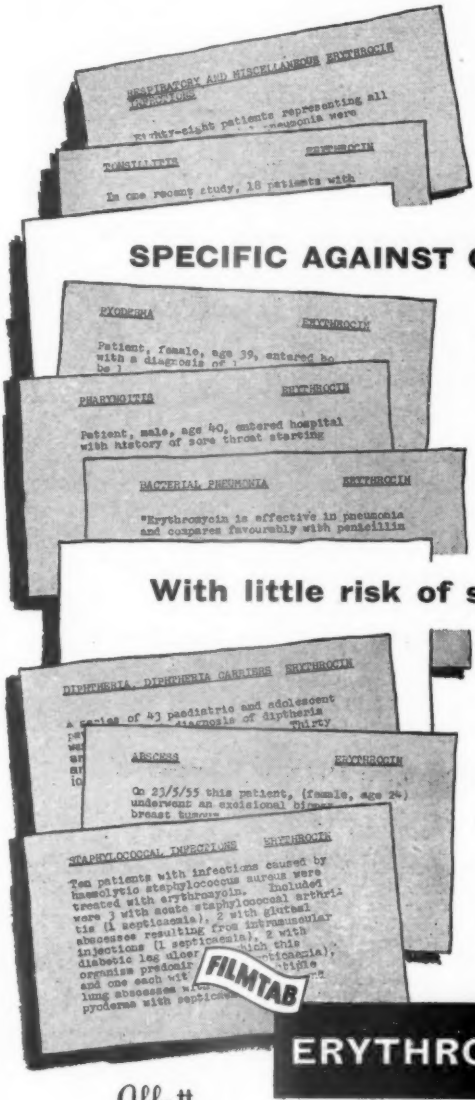

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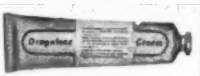

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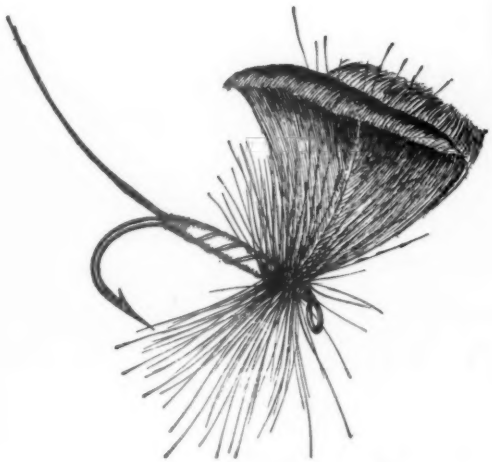

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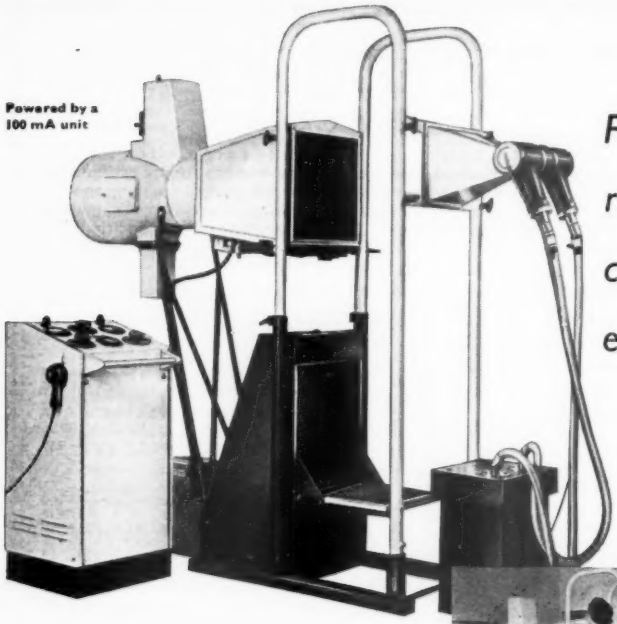
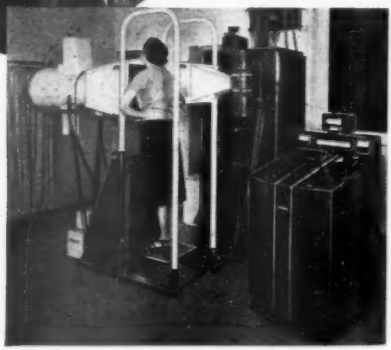


For fast, routine chest examinations

Powered by a 500 mA unit



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- **High diagnostic value with economy in film cost and storage**
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- **Automatic film identification**
- **Automatic exposure timing**
- **Interlocked for fool-proof operation**
- **Motor driven, time-saving patient stand**
- **X-ray tube always accurately centred**

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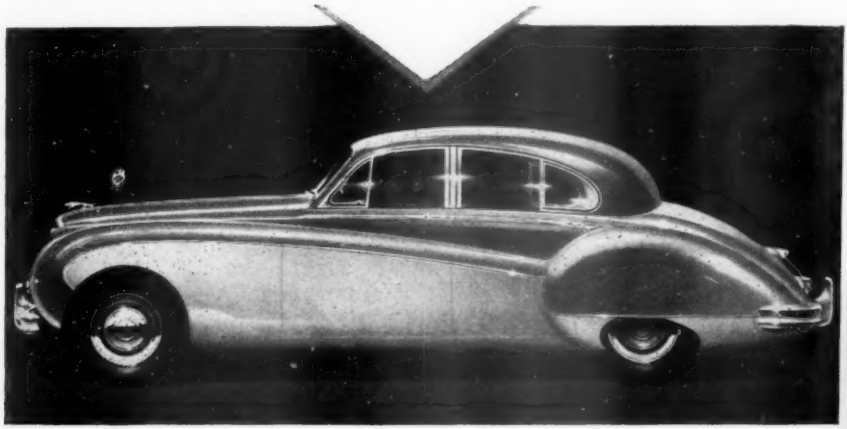
THE NEW JAGUAR

mark eight VIII



A new luxury model now joins the Jaguar range

Here to join the world famous Mark VII, XK and 2.4 litre models is the Mark Eight—one of the most luxurious models ever offered as a series production car. Interior furnishings, cabinet work, fitments and accessories are in the tradition of refinement and craftsmanship usually associated only with the art of specialist coachbuilders, whilst a degree of mechanical refinement has been achieved which stamps this car as outstanding even amongst the distinguished Jaguar range which it now joins.

Whilst preserving the basic lines of the Mark VII, the Mark Eight has its own distinctive frontal appearance and is offered in a wide range of two-tone exterior colours. It is available either with Automatic Transmission or Overdrive, or with normal manually-operated gearbox. Amongst the many interior refinements are flush-folding occasional tables in the rear compartment, hand-finished polished walnut fittings, deep pile rugs and extra-deep luxurious Dunlopillo cushions upholstered in specially selected fine grain soft-tanned leather.

MECHANICAL ADVANCES *include new cylinder head and induction system with type HD6 SU carburetters and twin exhausts. An important advance in the operation of the Automatic Transmission system is the fingertip control which enables the intermediate gear to be held indefinitely, and a new brake pedal layout permitting the use of either left or right foot.*

The current range of Mark VII, 2.4 and XK 140 models continues for 1957

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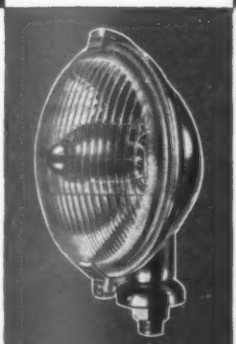
Safe driving under all conditions

SFT 576 'FLAT-TOPPED' BEAM FOGLAMP

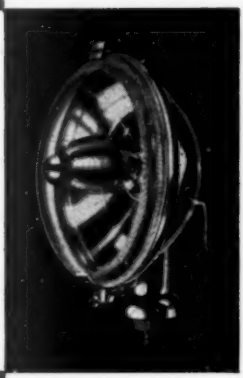
This attractive and highly efficient shallow bodied Foglamp is ideally suited for fitting in the restricted frontal space of the modern car. Although less than 6" in diameter, it incorporates the Lucas block-pattern lens which gives a wide spread "flat-topped" beam without upward or back glare. 82/6



SLR 576 LONG RANGE DRIVING LAMP

Similar in appearance this model is intended for use as a matched pair with the Foglamp SFT 576. It projects a powerful, concentrated thin pencil beam of 80,000 candle power, which makes an admirable driving beam for safe night driving. 82/6

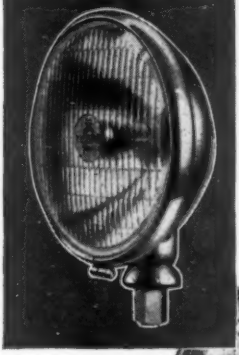
Price per pair—SFT & SLR 576, complete £7. 15. 0d.



SLR 700S LONG RANGE DRIVING LAMP

Intended for use in conjunction with, and to increase the range of the car's normal headlamps. Indispensable for safe, fast, night driving. The specially designed conical bulb shield and crystal clear lens, condenses all the light power into an intense 100,000 candle power pencil beam. 105/-

Price per pair—SFT & SLR 700S complete £9. 5. 0d.



SFT 700S 'FLAT-TOPPED' BEAM FOGLAMP

Incorporating the famous Lucas block pattern lens and 'Flat-Topped' beam, which gives an exceptionally wide spread of light without upward or back glare. With the SLR 700S Long Range Driving Lamp, it makes a powerful matched pair of auxiliary lamps for all weather conditions. 92/6

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All weather

LUCAS

TWINLAMPS

All lamps supplied complete with cable, switch and brackets.

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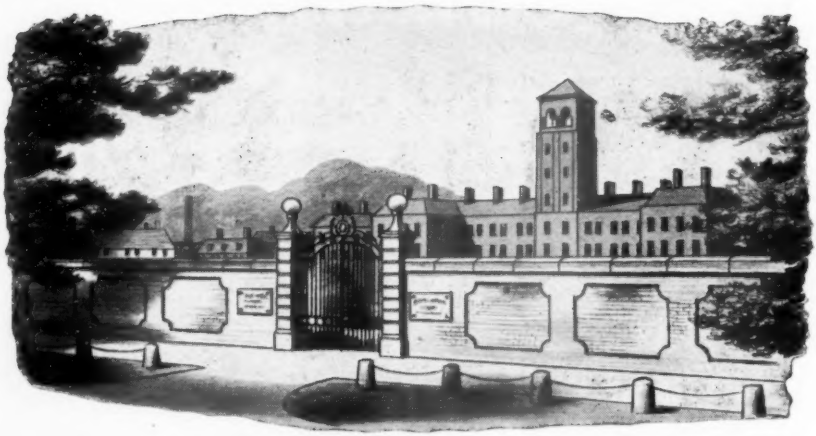

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*TRADE MARK

MEPROBAMATE

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MILTOWN is the one tranquillizer that relaxes both mind and body

MILTOWN Meprobamate is 2-methyl-2-n-propyl-1, 3-propanediol dicarbamate.

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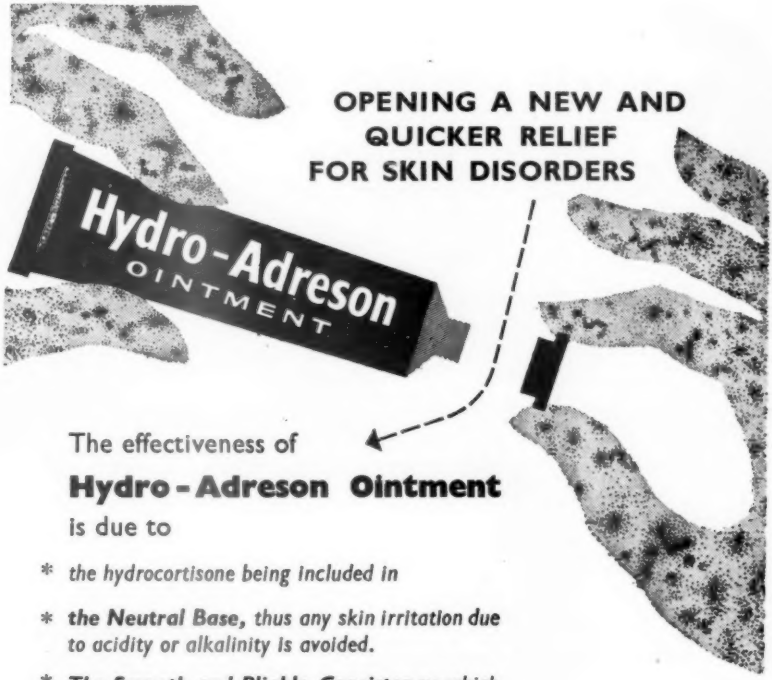

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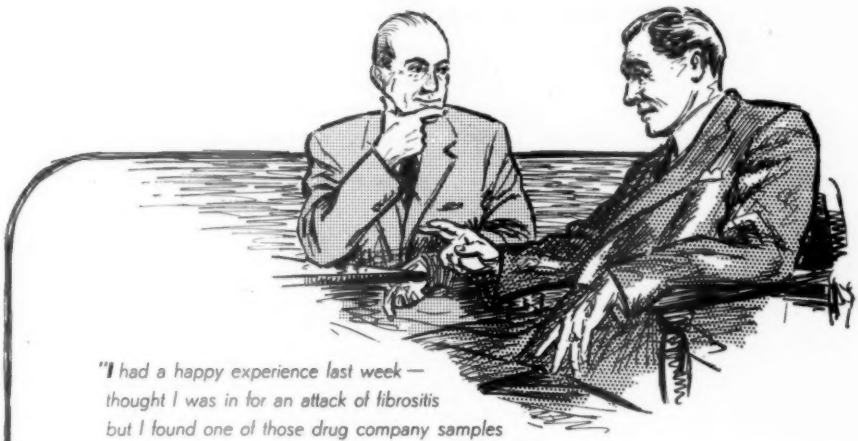

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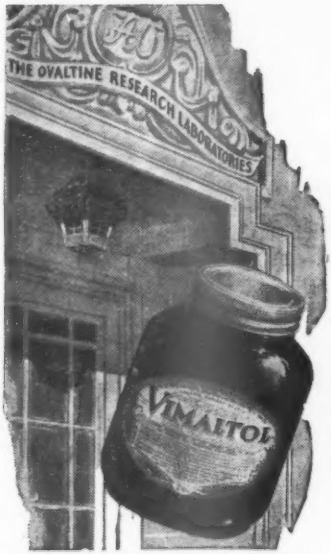

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